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=> d his ful

     FILE 'HCAPLUS' ENTERED AT 16:10:58 ON 28 JAN 2005
                  E DETMAR MICHAEL/AU
L1             86 SEA ABB=ON  ("DETMAR M"/AU OR "DETMAR MICHAEL"/AU OR "DETMAR
                  MICHAEL J"/AU)
                  E VACANTI JOSEPH P/AU
L2             83 SEA ABB=ON  ("VACANTI JOSEPH"/AU OR "VACANTI JOSEPH P"/AU OR
                  "VACANTI JOSEPH P M D"/AU)
                  E STREIT MICHAEL/AU
L3             20 SEA ABB=ON  "STREIT MICHAEL"/AU
                  E STEPHEN ANTONIA E/AU
L4              7 SEA ABB=ON  "STEPHEN ANTONIA E"/AU
L5              2 SEA ABB=ON  L1 AND L2 AND L3 AND L4
L6                ANALYZE L5 1-2 CT :      34 TERMS

     FILE 'REGISTRY' ENTERED AT 16:15:59 ON 28 JAN 2005
                  E THROMBOSPONDIN-2/CN
                  E THROMBOSPONDIN 2/CN
                  E TSP-2/CN
                  E TSP 2/CN
L7              1 SEA ABB=ON  "TSP 2"/CN

     FILE 'HCAPLUS' ENTERED AT 16:17:27 ON 28 JAN 2005
L8            275 SEA ABB=ON  (?THROMBOSPONDIN?(W)2 OR TSP(W)2 OR TSP2)
L9             65 SEA ABB=ON  L8 AND (?CELL?(W)?MATRIX? OR ?IMPLANT? OR ?GRAFT?)
L10             3 SEA ABB=ON  L9 AND (?PROCOLLAGEN? OR ?TYPE?(W)I(W)?REPEAT?)
L11            42 SEA ABB=ON  L9 AND (?ANGIOGENESIS? OR ?NEOPLASIA? OR ?VASCULAR?
                   OR ?BLOOD?(W)?VESSEL? OR ?INFLAM? OR (?CELL? OR ?SKIN?)(4A)?PR
                  OLIF? OR ?ENDIOMET? OR ?ANGIOGEN?(3A)(EYE? OR ?OCUL?) OR
                  ?RESTENOSIS? OR ?INFECT? OR ?ANTITUMOR?)
L12            41 SEA ABB=ON  L11 AND (?MATRIX? OR ?FIBRE? OR ?FIBROUS? OR
                  ?POLYMER? OR ?MICRO?)
L13             1 SEA ABB=ON  L12 AND (?HYDROGEL? OR ?SUBSTRAT?)
L14            41 SEA ABB=ON  L12 AND (?CELL? OR ?FIBROBLAST? OR ?TISSUE?(W)?SPEC
                  ? OR ?PROGENITOR? OR ?STEM?)
L15             2 SEA ABB=ON  L12 AND ?GENETIC?(W)?ENGINEER?
L16            30 SEA ABB=ON  L12 AND (?EXPRES? OR ?DIFFERENT? OR ?NATURAL?)
L17            41 SEA ABB=ON  L12 OR L13 OR L14 OR L15 OR L16
L18            24 SEA ABB=ON  L17 AND (PRD<20010330 OR PD<20010330)

     FILE 'MEDLINE, BIOSIS, EMBASE, JAPIO, JICST-EPLUS' ENTERED AT 16:23:18 ON
     28 JAN 2005
L19           119 SEA ABB=ON  L17
L20            58 DUP REMOV L19 (61 DUPLICATES REMOVED)
L21            36 SEA ABB=ON  L20 AND HUMAN?
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24 cits from CAPlus

36 cits from other db's

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=> d que stat l18
L8          275 SEA FILE=HCAPLUS ABB=ON  (?THROMBOSPONDIN?(W)2 OR TSP(W)2 OR
                TSP2)
L9           65 SEA FILE=HCAPLUS ABB=ON  L8 AND (?CELL?(W)?MATRIX? OR ?IMPLANT?
                 OR ?GRAFT?)
L11          42 SEA FILE=HCAPLUS ABB=ON  L9 AND (?ANGIOGENESIS? OR ?NEOPLASIA?
                OR ?VASCULAR? OR ?BLOOD?(W)?VESSEL? OR ?INFLAM? OR (?CELL? OR
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                ?OCUL?) OR ?RESTENOSIS? OR ?INFECT? OR ?ANTITUMOR?)
L12          41 SEA FILE=HCAPLUS ABB=ON  L11 AND (?MATRIX? OR ?FIBRE? OR
                ?FIBROUS? OR ?POLYMER? OR ?MICRO?)
L13           1 SEA FILE=HCAPLUS ABB=ON  L12 AND (?HYDROGEL? OR ?SUBSTRAT?)
L14          41 SEA FILE=HCAPLUS ABB=ON  L12 AND (?CELL? OR ?FIBROBLAST? OR
                ?TISSUE?(W)?SPEC? OR ?PROGENITOR? OR ?STEM?)
L15           2 SEA FILE=HCAPLUS ABB=ON  L12 AND ?GENETIC?(W)?ENGINEER?
L16          30 SEA FILE=HCAPLUS ABB=ON  L12 AND (?EXPRES? OR ?DIFFERENT? OR
                ?NATURAL?)
L17          41 SEA FILE=HCAPLUS ABB=ON  L12 OR L13 OR L14 OR L15 OR L16
L18          24 SEA FILE=HCAPLUS ABB=ON  L17 AND (PRD<20010330 OR PD<20010330)

=> d ibib abs l18 1-24

L18 ANSWER 1 OF 24  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2003:348686  HCAPLUS
DOCUMENT NUMBER:          138:358524
TITLE:                    Implantable medical devices having coated
                          indentations
INVENTOR(S):              Baker, Aaron B.; Sanders, Joan E.
PATENT ASSIGNEE(S):       University of Washington, USA
SOURCE:                   U.S., 14 pp.
                          CODEN: USXXAM
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     --------------       ----   --------    --------------------    --------
     US 6558422            B1    20030506    US 2000-532855          20000322 <--
PRIORITY APPLN. INFO.:                       US 1999-126545P      P  19990326 <--
AB   In one aspect the present invention provides indented structures that each
     include (a) a body defining a plurality of indentations, substantially all
     of the plurality of indentations including a surface layer including a
     biol. active substance; and (b) a body surface, wherein each of the
     plurality of indentations opens onto the body surface through a plurality
     of openings, and wherein the biol. active substance is not substantially
     present on the body surface. Examples of structures of the present
     invention include medical devices, such as medical devices that are
     completely or partially implantable into a living body. The
     surface layer of the indentations (or at least some of the indentations)
     of the medical devices of the invention may include biol. active mols.,
     such as proteins, that promote the growth of cells into and/or
     within the indentations, thereby promoting the acceptance of the
     implanted device by the living body. In another aspect, the
     present invention provides methods for making indented structures. SPARC
     was immobilized on surface modified polymer surfaces and was
     expected to promote angiogenesis and reduce fibrous
     capsule, while Thrombospondin 2 was expected to reduce
     both measurements. The expected trends in encapsulation and
     angiogenesis were observed
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REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 2 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:196148 HCAPLUS
DOCUMENT NUMBER: 137:237653
TITLE: Regulation of **angiogenesis** and **matrix** remodeling by localized, **matrix** -mediated antisense gene delivery
AUTHOR(S): Kyriakides, Themis R.; Hartzel, Tristan; Huynh, Grace; Bornstein, Paul
CORPORATE SOURCE: Department of Biochemistry, University of Washington, Seattle, WA, 98195, USA
SOURCE: Molecular Therapy (**2001**), 3(6), 842-849
CODEN: MTOHCK; ISSN: 1525-0016
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Implantation** of biomaterials, such as glucose sensors, leads to the formation of a poorly **vascularized** collagenous capsule that can lead to **implant** failure. This process, known as the foreign body reaction (FBR), develops in response to almost all biomaterials and consists of overlapping phases similar to those in wound healing. **Implantation** of porous biomaterials, such as polyvinyl alc. sponges, also leads to granuloma formation within the interstices of the sponge prior to encapsulation by the FBR. We asked whether delivery of an antisense cDNA for the potent **angiogenesis** inhibitor thrombospondin (**TSP**) **2** would enhance **blood vessel** formation and alter collagen fibrillogenesis in the sponge granuloma and capsule. Collagen solns. were mixed with plasmid to generate gene-activated **matrixes** (GAMs) and applied to biomaterials that were then **implanted** s.c. Sustained **expression** of plasmid-encoded proteins was observed at 2 wk and a month following **implantation.** In vivo delivery of plasmids, encoding either sense or antisense **TSP2** cDNA, altered **blood vessel** formation and collagen deposition in **TSP2**-null and wild-type mice, resp. Untreated **implants**, **implanted** next to GAM-treated **implants**, did not show exogenous gene **expression** and did not elicit altered responses, suggesting that gene delivery was limited to **implant** sites. This method of antisense DNA delivery has the potential to improve the performance and life span of **implantable** delivery devices and biosensors. (c) 2001 Academic Press.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 3 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:143280 HCAPLUS
DOCUMENT NUMBER: 136:189386
TITLE: Delivery of thrombospondin from **implantable** tissue matrices
INVENTOR(S): Detmar, Michael; Vacanti, Joseph P.; Streit, Michael; Stephen, Antonia E.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 16 pp., Cont.-in-part of U.S. Ser. No. 536,087.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
US 2002022592	A1	20020221	US 2001-822161		20010330	<--
US 2002031500	A1	20020314	US 2001-770339		20010126	<--
US 6692738	B2	20040217				
US 2004086497	A1	20040506	US 2003-690077		20031021	<--
PRIORITY APPLN. INFO.:			US 1999-127221P	P	19990331	<--
			US 2000-178842P	P	20000127	<--
			US 2000-536087	A2	20000324	<--
			US 2001-770339	A2	20010126	<--

AB Normal **cells**, such as **fibroblasts** or other tissue or organ **cell** types, are **genetically engineered** to **express** biol. active, anti-angiogenic compds., in particular, **thrombospondin-2**. These **cells** are seeded into a **matrix** for **implantation** into the patient to be treated. **Cells** may also be engineered to include a lethal gene, so that **implanted cells** can be destroyed once treatment is completed. **Cells** can be **implanted** in a variety of **different polymer matrixes**. In a preferred embodiment, these **matrixes** are **implantable** and biodegradable over a period of time equal to or less than the expected period of treatment, during which the **engrafted cells** form a functional tissue producing the desired biol. active agent for longer periods of time. These devices and strategies are used as delivery **systems**, which may be **implanted** by standard or minimally invasive **implantation** techniques, for delivery of anti-angiogenic mols., especially **thrombospondin-2**, for the treatment of a variety of conditions that produce abnormal growth, including treatment of malignant and benign **neoplasias**, **vascular** malformations (hemangiomas), **inflammatory** conditions, keloid formation and adhesion, endometriosis, congenital or endocrine abnormalities, and other conditions that can produce abnormal growth such as **infection**. **Bioimplants** maintained **TSP-2** secretion over prolonged time periods, resulting in a potent inhibition of tumor growth and **angiogenesis** of three **different**, highly aggressive malignant tumors **implanted** at a distant site.

L18 ANSWER 4 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:107136 HCAPLUS
DOCUMENT NUMBER: 136:156457
TITLE: Methods and devices to modulate the wound response by **thrombospondin 2** or osteopontin
INVENTOR(S): Bornstein, Paul; Kyriakides, Themis; Ratner, Buddy; Giachelli, Cecilia; Martinson, Laura; Scatena, Marta
PATENT ASSIGNEE(S): University of Washington, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 2002009735	A2	20020207	WO 2001-US24147	20010731	<--
WO 2002009735	A3	20021003			

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US,
UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002048577 A1 20020425 US 2001-919770 20010731 <--
PRIORITY APPLN. INFO.: US 2000-222071P P 20000801 <--

AB The invention provides methods of modulating the amount and/or biol. activity of **thrombospondin 2** or osteopontin in an animal. The methods comprise the step of introducing into the animal an amount of osteopontin, and/or a **thrombospondin** (**2**) antagonist, effective to modulate the amount or biol. activity of **thrombospondin** (**2**) or osteopontin in the animal. In another aspect, the invention provides medical devices comprising (a) a device body; and (b) a surface layer attached to the device body, the surface layer including an amount of an agents or antagonist of a **matricellular** protein sufficient to reduce the foreign body response against the medical device, wherein the medical device is adapted to be affixed to, or **implanted** within, the soft tissue of an animal.

L18 ANSWER 5 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:784465 HCAPLUS
DOCUMENT NUMBER: 136:292624
TITLE: Altered **extracellular matrix** remodeling and **angiogenesis** in sponge granulomas of **thrombospondin 2** -null mice
AUTHOR(S): Kyriakides, Themis R.; Zhu, Yu-Hong; Yang, Zhantao; Huynh, Grace; Bornstein, Paul
CORPORATE SOURCE: Department of Biochemistry, University of Washington, Seattle, WA, 98195, USA
SOURCE: American Journal of Pathology (**2001**), 159(4), 1255-1262
CODEN: AJPAA4; ISSN: 0002-9440
PUBLISHER: American Society for Investigative Pathology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **matricellular angiogenesis** inhibitor, thrombospondin (**TSP**) **2**, was shown to be an important modulator of wound healing and the foreign body response. Specifically, **TSP2**-null mice display improved healing with minimal scarring and form well-**vascularized** foreign body capsules. In this study the authors performed s.c. **implantation** of sponges and investigated the resulting angiogenic and fibrogenic responses. Histol. and immunohistochem. anal. of sponges, excised at 7, 14, and 21 days after **implantation**, revealed significant differences between **TSP2**-null and wild-type mice. Most notably, **TSP2**-null mice exhibited increased **angiogenesis** and fibrotic encapsulation of the sponge. However, invasion of dense tissue was compromised, even though its overall d. was increased. Furthermore, histomorphometry and biochem. assays demonstrated a significant increase in the **extracellular** distribution of **matrix** metalloproteinase (MMP) 2, but no change in the levels of active transforming growth factor-β1. The alterations in **neovascularization**, dense tissue invasion, and MMP2 in **TSP2**-null mice coincided with the deposition of **TSP2** in the **extracellular matrix**

of wild-type animals. These observations support the proposed role of **TSP2** as a modulator of **angiogenesis** and **matrix** remodeling during tissue repair. In addition, they provide in vivo evidence for a newly proposed function of **TSP2** as a modulator of **extracellular** MMP2 levels.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 6 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:675279 HCAPLUS
DOCUMENT NUMBER: 136:31314
TITLE: Antisense oligonucleotide ISIS 2922 targets IE-**expression** and prevents HCMV-IE-induced suppression of TSP-1 and **TSP-2 expression**
AUTHOR(S): Margraf, S.; Bittoova, M.; Vogel, J-U.; Kotchekov, R.; Doerr, H. W.; Cinatl, J., Jr.
CORPORATE SOURCE: Inst. f. Med. Virology, J. W. Goethe University Hospital, Frankfurt am Main, D-60596, Germany
SOURCE: Nucleosides, Nucleotides & Nucleic Acids (**2001**), 20(4-7), 1425-1428
CODEN: NNNAFY; ISSN: 1525-7770
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB ISIS 2922, but not ganciclovir (GCV), inhibits HCMV immediate early protein (IE) **expression** in **different infected cell** lines and prevents down-modulation of **extracellular matrix** proteins thrombospondin-1 and -2 induced by IE proteins. While action of ISIS 2922 is mainly due to specific inhibition of IE 2 mRNA, there is also evidence for unspecific effects in terms of inhibition of virus adhesion and penetration.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 7 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:628435 HCAPLUS
DOCUMENT NUMBER: 136:245113
TITLE: Thrombospondins and tumor **angiogenesis**
AUTHOR(S): de Fraipont, F.; Nicholson, A. C.; Feige, J.-J.; Van Meir, E. G.
CORPORATE SOURCE: Commissariat a l'Energie Atomique, Dept of Molecular and Structural Biology, INSERM EMI 0105, Grenoble, Fr.
SOURCE: Trends in Molecular Medicine (**2001**), 7(9), 401-407
CODEN: TMMRCY; ISSN: 1471-4914
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The thrombospondins (TSPs) are a family of five secreted proteins that are widely distributed in the **extracellular matrix** of numerous tissues. TSPs are multimodular and each domain specifies a distinct biol. function through interaction with a specific receptor. TSP1 and **TSP2** have anti-angiogenic activity, which, at least for TSP1, involves interaction with the **microvascular** endothelial **cell** receptor CD36. **Expression** of TSP1 and **TSP2** is modulated by hypoxia and by oncogenes. In several tumors (thyroid, colon, bladder carcinomas), TSP1 **expression** is inversely correlated with tumor grade and survival rate, whereas in others (e.g. breast carcinomas), it is correlated with the stromal response and

is of little prognostic value. Recent studies suggest that TSPs or TSP-derived peptides retaining biol. activity could be developed into promising new therapeutic strategies for the anti-angiogenic treatment of solid tumors.

REFERENCE COUNT: 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 8 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:294497 HCAPLUS
DOCUMENT NUMBER: 135:301809
TITLE: Upregulated **expression** of **angiogenesis** genes and down regulation of **cell** cycle genes in human colorectal cancer tissue determined by cDNA macroarray
AUTHOR(S): Tsunoda, Takuya; Nakamura, Takashi; Ishimoto, Kiwao; Yamaue, Hiroki; Tanimura, Hiroshi; Saijo, Nagahiro; Nishio, Kazuto
CORPORATE SOURCE: Second Department of Surgery, Wakayama Medical School, Wakayama, 641-0012, Japan
SOURCE: Anticancer Research (**2001**), 21(1A), 137-143
CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: International Institute of Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **differential expression** of hundreds of tightly, transcriptionally controlled genes in isolated human colorectal cancer and resp. normal mucosa from two patients was analyzed by the cDNA macroarray technique. MRNA prepared from the colorectal cancer tumors was compared with 588 genes spotted onto the filter. Case A showed down-regulation of the **expression** of **cell**-cycle-related genes including cyclins, cyclin-dependent kinase (CDK) 2, and CDK-activating kinase, as compared with normal mucosa from the same patient. The tumors showed up-regulation of **expression** of **angiogenesis**-related genes such as type II cytoskeletal 8 keratin, metalloproteinase subtypes, VEGF, and bFGF, to over 5-fold the levels in normal mucosa. Thus, colorectal carcinoma tissues are characterized by the upregulation of mols. related with **angiogenesis.** These results suggest that **angiogenesis**-related mols. are suitable candidates for target-based therapies for colorectal cancer patients. In case B, the largest difference in **expression** between the tumor and mucosal tissues was observed in the MMP-1 gene. In contrast to the first case, there was no increase in **expression** of **angiogenesis**-related mols. or decrease in **expression** of **cell** -cycle-regulatory mols. The **expression** profile was quite **different** between these two patients. This approach may eventually provide a mean of selecting target-based drugs in individual colon cancer patients.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 9 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:286053 HCAPLUS
DOCUMENT NUMBER: 135:42299
TITLE: Thrombospondins as **matricellular** modulators of **cell** function
AUTHOR(S): Bornstein, Paul
CORPORATE SOURCE: Departments of Biochemistry and Medicine, University of Washington, Seattle, WA, 98195, USA
SOURCE: Journal of Clinical Investigation (**2001**), 107(8), 929-934

CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 38 refs., on the role of TSP1 and **TSP2** proteins in platelet function, **cell-matrix** adhesion, motility, and chemotaxis, wound healing, the **inflammatory** reaction, TGF-P1, and angioinhibitory and **antitumor** activities.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 10 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:216353 HCAPLUS
DOCUMENT NUMBER: 134:308545
TITLE: **Extracellular matrix** metalloproteinase 2 levels are regulated by the low density lipoprotein-related scavenger receptor and **thrombospondin 2**
AUTHOR(S): Yang, Zhantao; Strickland, Dudley K.; Bornstein, Paul
CORPORATE SOURCE: Department of Biochemistry, The University of Washington, Seattle, WA, 98195, USA
SOURCE: Journal of Biological Chemistry (**2001**), 276(11), 8403-8408
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have recently shown that the adhesive defect observed in dermal **fibroblasts** derived from **thrombospondin 2** (**TSP2**)-null mice results from an increase in **matrix** metalloproteinase 2 (MMP2) levels. Adhesion was restored by replacement of **TSP2** and by inhibitors of MMP2 activity. In pursuing the observation that **TSP2** and MMP2 interact, we now demonstrate that this interaction is required for optimal clearance of **extracellular** MMP2 by **fibroblasts.** Since **TSP2** is known to be endocytosed by the scavenger receptor, low d. lipoprotein receptor-related protein (LRP), we determined whether interference with LRP function affected **fibroblast** adhesion and/or **extracellular** MMP2 levels. Addition of heparin, which competes for the binding of **TSP2** to LRP coreceptor proteoglycans, inhibited adhesion of control but not **TSP2**-null **cells**, and a blocking antibody to LRP as well as the LRP inhibitor, receptor-associated protein, also inhibited adhesion and increased MMP2 levels only in control **fibroblasts. TSP2** did not inhibit active MMP2 directly and did not inhibit the activation of pro-MMP2. Finally, the internalization of 125I-MMP2 was reduced in **TSP2**-null compared with control **fibroblasts.** We propose that clearance of MMP2-**TSP2** complexes by LRP is an important mechanism for the regulation of **extracellular** MMP2 levels in **fibroblasts**, and perhaps in other **cells.** Thus, some features of the phenotype of **TSP2**-null mice, such as abnormal collagen fibrillogenesis, accelerated wound healing, and increased **angiogenesis**, could result in part from increased MMP2 activity.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 11 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:103681 HCAPLUS
DOCUMENT NUMBER: 135:44240

TITLE: **Thrombospondin 2** modulates collagen fibrillogenesis and **angiogenesis**
AUTHOR(S): Bornstein, Paul; Kyriakides, Themis R.; Yang, Zhantao; Armstrong, Lucas C.; Birk, David E.
CORPORATE SOURCE: Department of Biochemistry, University of Washington, Seattle, WA, 98195, USA
SOURCE: Journal of Investigative Dermatology Symposium Proceedings (**2000**), 5(1), 61-66
CODEN: JDSPFO; ISSN: 1087-0024
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 28 refs. **Thrombospondin 2** (**TSP2**)-null mice, generated by targeted disruption of the Thbs2 gene, display a complex phenotype that is characterized, in part, by a variety of connective tissue abnormalities and increased **vascular** d. in skin and s.c. tissues. In this paper we summarize the evidence that **TSP2** functions as a **matricellular** protein to influence **cell** function by modulating **cell-matrix** interactions, rather than acting as an integral component of the **matrix.** Thus, the structurally abnormal collagen fibrils detected in skin appear to be the consequence of the defective adhesion demonstrated by dermal **fibroblasts** in culture that, in turn, result from increased **matrix** mmetalloproteinase 2 (MMP2, gelatinase A) production by these **cells.** Corroborating evidence for such a mode of action comes from transmission electron **microscopic** images of developing flexor muscle tendons that show distinct abnormalities in **fibroblast**-collagen fibril interactions in **TSP2**-null tissue. The increased **vascular** d. seen in skin of **TSP2**-null mice can be reproduced in a number of models of injury, including s.c. **implantation** of polyvinyl alc. sponges and silicone rubber disks, and excisional skin wounds. Expts. are proposed to distinguish between a primarily endothelial **cell** vs. an **extracellular matrix** origin for the increased **angiogenesis** in **TSP2**-null mice.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 12 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:15456 HCAPLUS
DOCUMENT NUMBER: 134:174295
TITLE: **Thrombospondin 2**, a **matricellular** protein with diverse functions
AUTHOR(S): Bornstein, Paul; Armstrong, Lucas C.; Hankenson, Kurt D.; Kyriakides, Themis R.; Yang, Zhantao
CORPORATE SOURCE: Department of Biochemistry, Department of Medicine, University of Washington, Seattle, WA, 98195, USA
SOURCE: Matrix Biology (**2000**), 19(7), 557-568
CODEN: MTBOEC; ISSN: 0945-053X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB Thrombospondin (**TSP**) **2** is a close relative of TSP1 but differs in its temporal and spatial distribution in the mouse. A review with approx. 70 refs. This difference in **expression** undoubtedly reflects the marked disparity in the DNA sequences of the promoters in the genes encoding the two proteins. The synthesis of **TSP2** occurs primarily in connective tissues of the developing and growing mouse. In the adult animal the protein is again produced in response to tissue injury and in association with the growth of tumors. Despite the

abnormalities in collagen fibrillogenesis, fragility of skin, and laxity of tendons and ligaments observed in the **TSP2**-null mouse, **TSP2** does not appear to contribute directly to the structural integrity of connective tissue elements. Instead, emerging evidence supports a mode of action of **TSP2** "at a distance", i.e. by modulating the activity and bioavailability of proteases and growth factors in the **pericellular** environment and, very likely, by interaction with **cell**-surface receptors. Thus, **TSP2** qualifies as a **matricellular** protein, as defined in the introduction to this minireview series. The phenotype of **TSP2** -null mice has been very helpful in providing clues to the functions of **TSP2.** In addition to histol. and functional abnormalities in connective tissues, these mice display an increased **vascularity** of the dermis and subdermal tissues, increased endosteal bone growth, a bleeding defect, and a marked adhesive defect of dermal **fibroblasts.** Our laboratory has established that **TSP2** binds **matrix** metalloproteinase 2 (MMP2) and that the adhesive defect in **TSP2**-null **fibroblasts** results from increased MMP2 activity. The investigation of the basis for the other defects in the **TSP2**-null mouse is likely to yield equally interesting results.

REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 13 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:722230 HCAPLUS
DOCUMENT NUMBER: 133:361647
TITLE: **Microglial** activation precedes acute neurodegeneration in Sandhoff disease and is suppressed by bone marrow transplantation
AUTHOR(S): Wada, Ryuichi; Tifft, Cynthia J.; Proia, Richard L.
CORPORATE SOURCE: Genetics of Development and Disease Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**2000**), 97(20), 10954-10959
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Sandhoff disease is a lysosomal storage disorder characterized by the absence of β-hexosaminidase and storage of GM2 ganglioside and related glycolipids in the central nervous **system.** The glycolipid storage causes severe neurodegeneration through a poorly understood pathogenic mechanism. In symptomatic Sandhoff disease mice, apoptotic neuronal **cell** death was prominent in the caudal regions of the brain. CDNA **microarray** anal. to monitor gene **expression** during neuronal **cell** death revealed an up-regulation of genes related to an **inflammatory** process dominated by activated **microglia.** Activated **microglial** expansion, based on gene **expression** and histol. anal., was found to precede massive neuronal death. Extensive **microglia** activation also was detected in a human case of Sandhoff disease. Bone marrow transplantation of Sandhoff disease mice suppressed both the explosive expansion of activated **microglia** and the neuronal **cell** death without detectable decreases in neuronal GM2 ganglioside storage. These results suggest a mechanism of neurodegeneration that includes a vigorous **inflammatory** response as an important component. Thus, this lysosomal storage disease has

parallels to other neurodegenerative disorders, such as Alzheimer's and prion diseases, where **inflammatory** processes are believed to participate directly in neuronal **cell** death.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 14 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:684044 HCAPLUS
DOCUMENT NUMBER: 134:187867
TITLE: Cytomegalovirus **infection** decreases **expression** of thrombospondin-1 and -2 in cultured human retinal glial **cells**: effects of antiviral agents
AUTHOR(S): Cinatl, Jindrich, Jr.; Bittoova, Martina; Margraf, Stefan; Vogel, Jens-Uwe; Cinatl, Jaroslav; Preiser, Wolfgang; Doerr, Hans Wilhelm
CORPORATE SOURCE: Zentrum der Hygiene, Institut fur Medizinische Virologie, Frankfurt am Main, D-60596, Germany
SOURCE: Journal of Infectious Diseases (**2000**), 182(3), 643-651
CODEN: JIDIAQ; ISSN: 0022-1899
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In **fibroblasts**, **infection** with human cytomegalovirus (HCMV) inhibits **expression** of the **extracellular matrix** proteins thrombospondin-1 and -2 (TSP-1 and **TSP-2**). These effects may depend on **expression** of HCMV immediate-early (IE) genes, which are activated by **cellular** transcription factor NF-κB. The influence of HCMV **infection** on TSP-1 and **TSP-2 expression** and the ability of **different** antiviral drugs to prevent these **cellular** changes in permissive cultures of human retinal glial **cells** were observed Ganciclovir inhibited only HCMV late antigen (LA) **expression**, whereas antisense oligonucleotide ISIS 2922 and peptide SN50, inhibitors of HCMV IE **expression** and NF-κB activity, resp., inhibited both IE and LA **expression.** ISIS 2922 and SN50, but not ganciclovir, prevented down-modulation of TSP-1 and **TSP-2.** The results showed that HCMV-induced down-modulation of TSP-1 and **TSP-2** in retinal glial **cells** is prevented by inhibition of HCMV IE **expression.** These findings may be relevant to pathogenesis and treatment of HCMV retinitis.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 15 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:355340 HCAPLUS
DOCUMENT NUMBER: 133:14982
TITLE: The role of thrombospondins 1 and 2 in **vascular** development
AUTHOR(S): Armstrong, Lucas C.; Kyriakides, Themis R.; Bornstein, Paul
CORPORATE SOURCE: Department of Biochemistry and Medicine, University of Washington, Seattle, WA, USA
SOURCE: Fetal and Neonatal Pulmonary Circulations (**2000**), 87-103. Editor(s): Weir, E. Kenneth; Archer, Stephen L.; Reeves, John T. Futura Publishing: Armonk, N. Y.
CODEN: 69AYA7

DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review with 74 refs. on thrombospondins 1 and 2 in the modulation of **angiogenesis** is given. Patterns of **expression**, effects on **cells** (endothelial **cells**, **fibroblasts**, **vascular** smooth muscle **cells**) in vitro, and **vascular** development in mice lacking thrombospondins 1 and 2 are described. Their interactions with TGF-β1 and **cell** surface receptors are reported. TSP1 modulates immune, epithelial, and endothelial **cells**. **TSP2** modulates the **cell-cell** and **cell-matrix** interactions of **fibroblasts**.
REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 16 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:763372 HCAPLUS
DOCUMENT NUMBER: 132:76690
TITLE: Accelerated wound healing in mice with a disruption of the **thrombospondin 2** gene
AUTHOR(S): Kyriakides, Themis R.; Tam, Jessica W. Y.; Bornstein, Paul
CORPORATE SOURCE: Department of Biochemistry, University of Washington, Seattle, WA, 98195, USA
SOURCE: Journal of Investigative Dermatology (**1999**), 113(5), 782-787
CODEN: JIDEAE; ISSN: 0022-202X
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mice that lack the **extracellular matrix** protein **thrombospondin 2** have, among several abnormalities, an increase in **vascular** d., abnormal collagen fibrils, and dermal **fibroblasts** that are defective in adhesion. These findings suggested that responses involving these processes, such as wound healing, might be altered. To investigate the healing process, excisional wounds were made with the aid of a biopsy punch. Such wounds, observed over a 14 day period, appeared to heal at an accelerated rate and with less scarring in **thrombospondin 2**-null mice. Histol. anal. of **thrombospondin 2**-null wound sites revealed the presence of an irregularly organized and highly **vascularized** granulation tissue. In addition, **thrombospondin 2**-null wounds retained a higher total **cellular** content, than control wounds. No differences in wound re-epithelization rates were observed, but **thrombospondin 2**-null epithelia formed rete pegs and were thicker than control epithelia. By immunohistochem., we detected elevated levels and an irregular deposition pattern for fibronectin in **thrombospondin 2**-null wounds, observations that correlated with the abnormal collagen organization in the granulation tissue. Immunostaining for **thrombospondin 2** in control wounds showed that the protein is present in both early and late wounds, in a scattered **cell**-associated pattern or widely distributed **cell**- and **matrix**-associated pattern, resp. Our results suggest that **thrombospondin 2** plays a crucial part in the organization and **vascularization** of the granulation tissue during healing, possibly by modulating **fibroblast-matrix** interactions in early wounds and regulating the extent of **angiogenesis** in late wounds.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 17 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:434297 HCAPLUS
DOCUMENT NUMBER: 131:240730
TITLE: The thrombospondins: multimodular proteins with **angiogenesis** inhibiting effects
AUTHOR(S): Feige, J. J.
CORPORATE SOURCE: Unite INSERM 244, Departement de Biologie Moleculaire et Structurale, CEA, Grenoble, 38054, Fr.
SOURCE: Pathologie Biologie (**1999**), 47(4), 339-344
CODEN: PTBIAN; ISSN: 0031-3009
PUBLISHER: Expansion Scientifique Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: French
AB A review with 33 refs. The thrombospondins (TSPs) are a family of multimodular proteins that bind to the **extracellular matrix** with strong affinity. Of the five members of the TSP family, TSP1 and **TSP2** are the only ones that inhibit endothelial **cell** migration in vitro and **neoangiogenesis** in vivo. This **angiogenesis**-inhibiting effect is mediated by interaction of a short sequence in type I modules with the membrane receptor CD36. TSP1 and **TSP2** gene knockout expts. in mice showed increased **blood vessel** d. in **TSP2** -/- but no such alteration in TSP1 -/- animals. Loss of TSP1 gene **expression** was correlated with acquisition of an angiogenic phenotype in several models of human malignant tumors. Taken in concert, these findings suggest that TSP1 and, to a lesser extent, **TSP2** may have therapeutic potential as **angiogenesis**-inhibiting factors.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 18 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:368612 HCAPLUS
DOCUMENT NUMBER: 131:143072
TITLE: Mice that lack the **angiogenesis** inhibitor, **thrombospondin 2**, mount an altered foreign body reaction characterized by increased **vascularity**
AUTHOR(S): Kyriakides, Themis R.; Leach, Kathleen J.; Hoffman, Allan S.; Ratner, Buddy D.; Bornstein, Paul
CORPORATE SOURCE: Department of Biochemistry, University of Washington, Seattle, WA, 98195, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1999**), 96(8), 4449-4454
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Disruption of the **thrombospondin 2** gene (Thbs2) in mice results in a complex phenotype characterized chiefly by abnormalities in **fibroblasts**, connective tissues, and **blood vessels**. Consideration of this phenotype suggested to the authors that the foreign body reaction (FBR) might be altered in **thrombospondin 2** (**TSP2**)-null mice. To investigate the participation of **TSP2** in the FBR, polydimethylsiloxane (PDMS) and oxidized PDMS (ox-PDMS) disks were **implanted** in **TSP2**-null and control mice. Growth of **TSP2**-null and control skin **fibroblasts** in vitro also was evaluated on both types of disks. Normal **fibroblasts** grew as a

monolayer on both surfaces, but attachment of the **cells** to ox-PDMS was weak and sensitive to movement. **TSP2**-null **fibroblasts** grew as aggregates on both surfaces, and their attachment was further compromised on ox-PDMS. After a 4-wk **implantation** period, both types of PDMS elicited a similar FBR with a collagenous capsule in both **TSP2**-null and control mice. However, strikingly, the collagenous capsule that formed in **TSP2** -null mice was highly **vascularized** and thicker than that formed in normal mice. In addition, abnormally shaped collagen fibers were observed in capsules from mutant mice. Thus, the presence or absence of an **extracellular matrix** component, **TSP2**, can influence the nature of the FBR, in particular its **vascularity.** The **expression** of **TSP2** therefore could represent a mol. target for local inhibitory measures when **vascularization** of the tissue surrounding an **implanted** device is desired.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 19 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:725903 HCAPLUS
DOCUMENT NUMBER: 130:62615
TITLE: Two-hybrid analysis reveals multiple direct interactions for thrombospondin 1
AUTHOR(S): Aho, Sirpa; Uitto, Jouni
CORPORATE SOURCE: Department of Dermatology and Cutaneous Biology and Department of Biochemistry and Molecular Pharmacology, Jefferson Medical College, and the Jefferson Institute of Molecular Medicine, Thomas Jefferson University, Philadelphia, PA, USA
SOURCE: Matrix Biology (**1998**), 17(6), 401-412
CODEN: MTBOEC; ISSN: 0945-053X
PUBLISHER: Gustav Fischer Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The yeast two-hybrid **system** was used to reveal the interactions between proteins residing within the cutaneous basement membrane zone and other gene products **expressed** in cultured human keratinocytes. The proteins of interest included type VII collagen, the predominant component of anchoring fibrils, and laminin 5, a component of anchoring filaments. Although the two-hybrid **system** was not able to verify a direct interaction between the type VII collagen NC1 domain and the short arm of Lamβ3, the type VII collagen NC1 domain (tVII/NC1) and the laminin 5 β3 chain globular domain VI (lam5/β3) cDNAs, when used as baits, detected four overlapping cDNA clones encoding thrombospondin 1 (TSP1). The overlapping region of these cDNAs encodes amino acids 400-459, a segment included within a 70 kDa chymotryptic fragment known to bind type V collagen, laminin-1 and other **matrix** components. The type VII collagen NC1/TSP1 interaction was confirmed by exchanging the vectors, and the interacting domain was mapped by testing a set of both 5' and 3' deletion constructs. The central region of TSP1, when used as a bait in two-hybrid **system**, showed strong binding to the fibronectin (FN) type III-like repeats 4-7 of type VII collagen NC1 domain. The TSP1 bait also interacted with laminin 5 β3 chain domain VIII, and the TSP1/laminin 5 β3 chain interaction was verified by a GST-fusion protein interaction assay. The transcripts encoding TSP1, **TSP2**, Lamβ3 and type VII collagen were abundant in cultured foreskin keratinocytes, and the **expression** of TSP1 and **TSP2** in a wide variety of adult and fetal tissues was confirmed by PCR anal. of multiple tissue cDNA panels. Furthermore, TSP1 type I

repeats showed self interaction, and recognized a clone for **extracellular matrix** protein fibrillin-2. In addition, clones encoding **angiogenesis** related protein Jagged1 and a platelet enzyme phospholipase scramblase were identified. Thus, the results indicate several previously undetected interactions of TSP1, which is known to be highly **expressed** during embryonic development, tissue remodeling and wound healing.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 20 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:586930 HCAPLUS
DOCUMENT NUMBER: 129:300449
TITLE: The distribution of the **matricellular** protein **thrombospondin 2** in tissues of embryonic and adult mice
AUTHOR(S): Kyriakides, Themis R.; Zhu, Yu-Hong; Yang, Zhantao; Bornstein, Paul
CORPORATE SOURCE: Dep. Biochem., Univ. Washington, Seattle, WA, 98195, USA
SOURCE: Journal of Histochemistry and Cytochemistry (**1998**), 46(9), 1007-1015
CODEN: JHCYAS; ISSN: 0022-1554
PUBLISHER: Histochemical Society, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mice that lack the **matricellular** protein **thrombospondin 2** (**TSP2**) develop a pleiotropic phenotype characterized by morphol. changes in connective tissues, an increase in **vascular** d., and a propensity for bleeding. Furthermore, dermal **cells** derived from **TSP2**-null mice display adhesion defects, a finding that implicates **TSP2** in **cell-matrix** interactions. To gain a better understanding of the participation of **TSP2** in the development and maturation of the mouse, we examined its distribution in embryonic and adult tissues. Special attention was paid to the presence of **TSP2** in collagen fibers, because collagen fibrils in the **TSP2**-null mouse appear to be irregular in size and contour by electron **microscopy.** Immunohistochem. anal. of Day 15 and Day 18 embryos revealed **TSP2** in areas of chondrogenesis, osteogenesis, and vasculogenesis, and in dermal and other connective tissue-forming **cells.** Distinctly **different** patterns of deposition of **TSP2** were observed in areas of developing cartilage and bone at Day 15 and 18 of embryonic development. A survey of adult tissues revealed **TSP2** in dermal **fibroblasts,** articular chondrocytes, Purkinje **cells** in the cerebellum, Leydig **cells** in the testis, and in the adrenal cortex. Dermal **fibroblasts** were also shown to synthesize **TSP2** in vitro. The distribution of **TSP2** during development is in keeping with its participation in the formation of a variety of connective tissues. In adult tissues, **TSP2** is located in the **pericellular** environment, where it can potentially influence the **cell-matrix** interactions associated with **cell** movement and tissue repair.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 21 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:424639 HCAPLUS
DOCUMENT NUMBER: 129:63073
TITLE: Hormonally regulated components of the adrenocortical

cell environment and the control of adrenal cortex homeostasis
AUTHOR(S): Feige, Jean-Jacques; Keramidas, M.; Chambaz, E. M.
CORPORATE SOURCE: Laboratoire Biochemie Regulations Cellulaires Endocrines, Departement Biologie Moleculaire Structurale, CEA Grenoble, Grenoble, F-38054, Fr.
SOURCE: Hormone and Metabolic Research (**1998**), 30(6/7), 421-425
CODEN: HMMRA2; ISSN: 0018-5043
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 42 refs. is given on the ongoing characterization of the structure and functions of the **extracellular matrix** components secreted by adrenocortical **cells** and their possible implication in the hormonal regulation of adrenal cortex homeostasis is discussed. The **extracellular matrix** (ECM) strongly contributes to the regulation of **cell proliferation** and **cell differentiation**, and thereby of embryonic development and adult tissue homeostasis. Fibronectin (FN) and laminin (LN) are both major adhesive proteins for adrenocortical **cells.** FN is synthesized by bovine fasciculata **cells** in primary culture, and its synthesis is stimulated by TGFβ1, TGFβ2, and FGF-2 but is not modified by IGF-1 or by the hormones ACTH and angiotensin II. LN is also synthesized by bovine fasciculata **cells** and its synthesis is specifically stimulated by ACTH. Both proteins are haptotactic and chemotactic for adrenocortical **cells**, suggesting a physiol. role in adrenocyte migration. Their distribution in the adrenal gland is quite distinct. LN is uniformly present in the steroidogenic **cells** from the 3 zones, whereas FN is abundant in the **fibrovascular** structures of the capsule and the cortex. ACTH treatment of adrenocortical **cells** strongly induces the **expression** and secretion of **thrombospondin-2** (**TSP2**), a large trimeric **matricellular** protein. The multimodular structure of **TSP2** is the support of a variety of biol. functions. **TSP2** promotes attachment but prevents spreading of adrenocortical **cells.** On the other hand, **TSP2** induces the activation of latent TGFβ through an indirect mechanism and is anti-angiogenic in vitro. The overall distribution of **TSP2** in the glomerulosa and fasciculata zones of the adrenal cortex, and its absence from the reticularis zone, argue in favor of a role in the protection of adrenocortical **cells** against apoptosis. In the adrenal cortex, 5 main biol. functions are potentially regulated by components of the **extracellular matrix**: **stem cell** commitment into the adrenocyte **differentiation** pathway, terminal **differentiation** toward the 3 distinct adrenocyte phenotypes, centripetal migration, apoptosis, and the formation of the capillary network. Future studies will aim at deciphering which **extracellular** component(s) is involved in each of these regulations.

L18 ANSWER 22 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:105685 HCAPLUS
DOCUMENT NUMBER: 126:210379
TITLE: Thrombospondin-1 and -2 messenger RNA **expression** in normal, benign, and neoplastic human breast tissues: correlation with prognostic factors, tumor **angiogenesis**, and **fibroblastic** desmoplasia

AUTHOR(S): Bertin, Nicolas; Clezardin, Philippe; Kubiak, Robert; Frappart, Lucien
CORPORATE SOURCE: Dep. of Pathology and CNRS UMR 5641 and INSERM Research Unit 403, Edouard Herriot Hospital, Lyon, 69437, Fr.
SOURCE: Cancer Research (**1997**), 57(3), 396-399
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Thrombospondin-1 (TSP1) is a Mr 450,000 **extracellular matrix** glycoprotein that modulates tumor growth, **angiogenesis**, and metastasis. Of the five structurally **different** TSPs described to date, only **TSP2** is similar to TSP1 in terms of its mol. architecture, and **TSP2** also modulates **angiogenesis. Angiogenesis** plays a relevant role in the biol. aggressiveness of breast cancer, and TSP1 is present in the tumor stroma (termed desmoplasia) of invasive human breast ductal carcinoma not otherwise specified (NOS). The present study was designed to identify and quantify TSP1 and **TSP2** mRNAs in normal, benign, and neoplastic human breast tissues using the reverse transcriptase PCR technique. The authors found that **TSP2**, like TSP1, was **expressed** in human breast tissues, and that TSP1 and **TSP2** mRNA **expression** in invasive breast carcinoma NOS was significantly increased compared to that observed in normal and benign tissues. The **expression** of TSP1 and **TSP2** in invasive breast ductal carcinoma NOS did not significantly correlate with any of the prognostic factors studied (tumor size, lymph node status, morphol., and hormone receptor status). However, when the authors' study population was divided according to the quantity of tumor stroma, TSP1 (and possibly **TSP2**) mRNA **expression** and **microvessel** counts in desmoplastic-rich stroma of breast carcinoma NOS were significantly increased compared to those observed in desmoplastic-poor stromata.
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 23 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:103007 HCAPLUS
DOCUMENT NUMBER: 120:103007
TITLE: **Differential expression** of thrombospondin 1, 2, and 3 during murine development
AUTHOR(S): Iruela-Arispe, M. Luisa; Liska, DeAnn J.; Sage, E. Helene; Bornstein, Paul
CORPORATE SOURCE: Dep. Biol. Struct., Univ. Washington, Seattle, WA, 98195, USA
SOURCE: Developmental Dynamics (**1993**), 197(1), 40-56
CODEN: DEDYEI; ISSN: 1058-8388
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Thrombospondin 1 is a secreted, trimeric glycoprotein that mediates interactions between **cells** and **extracellular matrix** and exhibits **cell**-specific effects on migration and proliferation. Recently, two addnl. thrombospondin genes (**thrombospondin 2** and 3) have been identified. To study the functions of these proteins, the authors have used in situ hybridization and RNase protection assays to compare the **expression** of the genes encoding thrombospondin 1, 2, and 3 during murine embryogenesis. Thrombospondin mRNAs were associated with ossification, neuronal organogenesis, and lung development, although transcripts were **differentially expressed.**

Thrombospondin 1 was predominant from days 10 to 13. During this period, high but transient levels of **expression** were observed in the neural tube, head mesenchyme, and cardiac cushions. In contrast, a more constant level of thrombospondin 1 mRNA was apparent in resident megakaryocytes of the liver, as well as in circulating megakaryocytes; neither **thrombospondin 2** nor 3 was detected in these **cells.** Thrombospondin 1 was also produced by **cells** of the developing kidney and gut. The **expression** of **thrombospondin 2** was confined principally to organized connective tissue that included pericardium, pleura, perichondrium, periosteum, meninges, ligaments, and reticular dermis. **Thrombospondin 2** was also produced by **differentiating** skeletal myoblasts and by **cells** of the kidney and gut. Moreover, high levels of **expression** were detected in **blood vessels.** Thrombospondin 3 mRNA was restricted to brain, cartilage, and lung. Although thrombospondin 1, 2, and 3 belong to a family of structurally related genes, the differences observed in the spatiotemporal distribution of the corresponding mRNAs indicate unique functions for these secreted proteins.

L18 ANSWER 24 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:163497 HCAPLUS
DOCUMENT NUMBER: 118:163497
TITLE: Characterization of mouse **thrombospondin 2** sequence and **expression** during **cell** growth and development
AUTHOR(S): Laherty, Carol D.; O'Rourke, Karen; Wolf, Frederick W.; Katz, Ronald; Seldin, Michael F.; Dixit, Vishva M.
CORPORATE SOURCE: Med. Sch., Univ. Michigan, Ann Arbor, MI, 48109, USA
SOURCE: Journal of Biological Chemistry (**1992**), 267(5), 3274-81
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Thrombospondin (TSP) is an **extracellular matrix** glycoprotein whose **expression** has been associated with a variety of **cellular** processes including growth and embryogenesis. The recent discovery of the existence of a second mouse TSP gene necessitates careful examination of the discrete biochem. and functional properties associated with each mol. In this report, the primary structures of human TSP, mouse TSP1 (mTSP1), mouse **TSP2** (mTSP2), and chicken TSP are compared; and the **expression** of mTSP1 and mTSP2 during embryogenesis and growth factor-mediated **cell proliferation** is examined The cloning and sequencing of the entire coding regions of mTSP1 and mTSP2 revealed considerable conservation of residues critical for TSP structure and function; these data suggest that **TSP2** is capable of trimer formation and many of the same **cell**-surface and ligand interactions that mediate TSP function. Comparison of the various TSP sequences also allowed the assignment based on sequence homol. of previously reported human TSP as TSP1 and chicken TSP as **TSP2.** The mTSP2, like mTSP1, was shown to be a primary response gene when quiescent Swiss 3T3 **cells** were stimulated with serum, platelet-derived growth factor BB, basic **fibroblast** growth factor, or interleukin-1β. Interestingly, TSP1 and **TSP2** exhibited markedly **different** tissue- and stage-specific patterns of mRNA **expression** during mouse embryogenesis, implying that the two TSP mols. possess discrete functional properties important for development. Addnl., the TSP genes (Thbs1 and Thbs2) were mapped to single loci on mouse chromosomes 2 and 17, resp.

```
=> d que stat l21
L8          275 SEA FILE=HCAPLUS ABB=ON  (?THROMBOSPONDIN?(W)2 OR TSP(W)2 OR
                TSP2)
L9           65 SEA FILE=HCAPLUS ABB=ON  L8 AND (?CELL?(W)?MATRIX? OR ?IMPLANT?
                 OR ?GRAFT?)
L11          42 SEA FILE=HCAPLUS ABB=ON  L9 AND (?ANGIOGENESIS? OR ?NEOPLASIA?
                OR ?VASCULAR? OR ?BLOOD?(W)?VESSEL? OR ?INFLAM? OR (?CELL? OR
                ?SKIN?)(4A)?PROLIF? OR ?ENDIOMET? OR ?ANGIOGEN?(3A)(EYE? OR
                ?OCUL?) OR ?RESTENOSIS? OR ?INFECT? OR ?ANTITUMOR?)
L12          41 SEA FILE=HCAPLUS ABB=ON  L11 AND (?MATRIX? OR ?FIBRE? OR
                ?FIBROUS? OR ?POLYMER? OR ?MICRO?)
L13           1 SEA FILE=HCAPLUS ABB=ON  L12 AND (?HYDROGEL? OR ?SUBSTRAT?)
L14          41 SEA FILE=HCAPLUS ABB=ON  L12 AND (?CELL? OR ?FIBROBLAST? OR
                ?TISSUE?(W)?SPEC? OR ?PROGENITOR? OR ?STEM?)
L15           2 SEA FILE=HCAPLUS ABB=ON  L12 AND ?GENETIC?(W)?ENGINEER?
L16          30 SEA FILE=HCAPLUS ABB=ON  L12 AND (?EXPRES? OR ?DIFFERENT? OR
                ?NATURAL?)
L17          41 SEA FILE=HCAPLUS ABB=ON  L12 OR L13 OR L14 OR L15 OR L16
L19         119 SEA L17
L20          58 DUP REMOV L19 (61 DUPLICATES REMOVED)
L21          36 SEA L20 AND HUMAN?

=> d ibib abs l21 1-36

L21  ANSWER 1 OF 36     MEDLINE on STN
ACCESSION NUMBER:   2004605385     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 15579451
TITLE:              Thrombospondin 2 functions as an
                    endogenous regulator of angiogenesis and
                    inflammation in rheumatoid arthritis.
AUTHOR:             Park Yong Wook; Kang Young Mo; Butterfield Joe; Detmar
                    Michael; Goronzy Jorg J; Weyand Cornelia M
CORPORATE SOURCE:   Department of Medicine, Lowance Center for Human
                    Immunology, Emory University School of Medicine, Atlanta,
                    GA 30322, USA.
CONTRACT NUMBER:    R01 AI 44142 (NIAID)
     R01 AR 41974 (NIAMS)
     R01 AR 42527 (NIAMS)
     R01 EY 11916 (NEI)
SOURCE:             American journal of pathology, (2004 Dec) 165 (6) 2087-98.
                    Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:        200501
ENTRY DATE:         Entered STN: 20041207
                    Last Updated on STN: 20050112
                    Entered Medline: 20050111
AB   Thrombospondin 2 (TSP2), a
     matricellular protein with a primary role in modulating
     cell-matrix interactions, has been implicated in tissue
     repair and foreign body responses.  Here we show that TSP2 has
     regulatory function in the chronic inflammatory lesions of
     rheumatoid arthritis.  Tissue TSP2, produced by synovial
     fibroblasts, endothelial cells, and macrophages
     correlated not only with the intensity of angiogenesis but also
     with the architecture of lymphoid infiltrates.  Synovial tissues with
     diffuse inflammatory infiltrates had high levels of TSP2
     , whereas synovial tissues with ectopic germinal center reactions and T
```

cell-B **cell** aggregates produced low levels. **Cell**-based gene therapy with **TSP2** was used to examine the in vivo effects of the **matrix** protein on **neoangiogenesis** and lymphoid organization. **Human** synovium-severe combined immunodeficiency (SCID) mouse chimeras were treated with **TSP2**-transfected **fibroblasts** deposited into the peritoneum. **Overexpression** of **TSP2** led to the accumulation of **TSP2** protein in the **inflamed** synovium and resulted in a prompt inhibition of lesional **vascularization.** Beside its anti-angiogenic activity, **TSP2** also suppressed the production of the **proinflammatory** mediators, interferon-gamma and tumor necrosis factor-alpha, and induced the depletion of tissue-residing T **cells.** We propose that **TSP2** is an endogenous regulator of **angiogenesis** and autoimmune **inflammation** in the synovium and represents a protective mechanism preventing ectopic lympho-organogenesis and persistent **inflammation** in this tissue site.

L21 ANSWER 2 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2004148971 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15041956
TITLE: **Microarray** analysis of gene **expression** in **human** donor sclera.
AUTHOR: Young Terri L; Scavello Genaro S; Paluru Prasuna C; Choi Jonathan D; Rappaport Eric F; Rada Jody A
CORPORATE SOURCE: Division of Ophthalmology, Children's Hospital of Philadelphia and the University of Pennsylvania, Philadelphia, PA 19104, USA.. youngt@email.chop.edu
CONTRACT NUMBER: EY00376 (NEI)
EY09391 (NEI)
EY121291 (NEI)
RR017703 (NCRR)
SOURCE: Molecular vision [electronic resource], (2004 Mar 22) 10 163-76.
Journal code: 9605351. ISSN: 1090-0535.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 20040326
Last Updated on STN: 20040413
Entered Medline: 20040412

AB PURPOSE: To develop gene **expression** profiles of **human** sclera to allow for the identification of novel, uncharacterized genes in this tissue-type, and to identify candidate genes for scleral disorders. METHODS: Total RNA was isolated from 6 donor sources of **human** sclerae, and reverse transcribed into cDNA using a T7-(dT) 24 primer. The resulting cDNA was in vitro transcribed to produce biotin-labeled cRNA, fragmented, and mixed with hybridization controls before a 16 h hybridization step with oligonucleotide probes on 6 Affymetrix U95A chips. The chips were scanned twice at 570 nM and the data collected using GeneChip software. Array analyses were carried out with **Microarray** Suite, version 5.0 (Affymetrix), using the **expression** analysis algorithm to run an absolute analysis after **cell** intensities were computed. All arrays were scaled to the same target intensity using all probe sets. Reverse-transcription **polymerase** chain reaction (RT-PCR) was performed to validate the **microarray** results. RESULTS: There were 3,751 genes with "present" calls assigned independently to all six **human** scleral

samples. These genes could be clustered into 4 major categories; transcription (10%), metabolism (8.8%), **cell** growth and **proliferation** (5.4%), and **extracellular matrix** (2%). Many **extracellular matrix** proteins, such as collagens 6A3 and 10A1, **thrombospondins** 2 and 4, and dystroglycan have not previously been shown to be **expressed** in sclera. RT-PCR results confirmed scleral **expression** in 7 **extracellular matrix** genes examined. CONCLUSIONS: This study demonstrated the utility of gene **microarray** technology in identifying global patterns of scleral gene **expression**, and provides an extended list of genes **expressed** in **human** sclera. Identification of genes **expressed** in sclera contributes to our understanding of scleral biology, and potentially provides positional candidate genes for scleral disorders such as high myopia.

L21 ANSWER 3 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2003594632 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14675207
TITLE: An N-terminal 80 kDa recombinant fragment of **human** **thrombospondin-2** inhibits **vascular** endothelial growth factor induced endothelial **cell** migration in vitro and tumor growth and **angiogenesis** in vivo.
AUTHOR: Noh Yun-Hee; Matsuda Kant; Hong Young-Kwon; Kunstfeld Rainer; Riccardi Lucia; Koch Manuel; Oura Hajimu; Dadras Soheil S; Streit Michael; Detmar Michael
CORPORATE SOURCE: Cutaneous Biology Research Center and Department of Dermatology, Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts 02129, USA.
CONTRACT NUMBER: CA69184 (NCI)
CA91861 (NCI)
CA92644 (NCI)
SOURCE: Journal of investigative dermatology, (2003 Dec) 121 (6) 1536-43.
Journal code: 0426720. ISSN: 0022-202X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20031217
Last Updated on STN: 20040130
Entered Medline: 20040129

AB We have previously shown that stable **overexpression** of the **thrombospondin-2** (**TSP-2**) gene inhibited the tumor growth and **angiogenesis** of **human** squamous **cell** carcinoma xenotransplants. To investigate the potential **antitumoral** efficacy of **systemic TSP** **-2** therapy, we **expressed** a recombinant 80 kDa fragment of **human TSP-2** (**TSP-2** /NTF), encompassing the N-terminal globular region through the three type 1 repeats, in **human** kidney 293 EBNA **cells**, using a modified pCEP4 **expression** vector. Daily intraperitoneal injections of **TSP-2**/NTF resulted in a significant inhibition of the growth of **human** A431 squamous **cell** carcinomas in vivo and in reduced tumor **vascularization.** To further investigate possible mechanisms of the antiangiogenic activity of **TSP-2**/NTF, several in vitro **angiogenesis** assays were performed in **human** dermal **microvascular** endothelial **cells.** **TSP-2**/NTF inhibited

vascular endothelial growth factor induced migration of **human** dermal **microvascular** endothelial **cells** and inhibited tube formation on Matrigel in vitro. **TSP-2**/NTF also inhibited **vascular** endothelial growth factor induced **angiogenesis** in an in vivo Matrigel assay. Moreover, **TSP-2**/NTF potently induced **human** dermal **microvascular** endothelial **cell** apoptosis in vitro but did not affect A431 tumor **cell proliferation** or apoptosis. These findings identify **TSP-2**/NTF as a potent **systemic** inhibitor of tumor growth and **angiogenesis**, acting by direct inhibition of several endothelial **cell** functions involved in **neovascularization.**

L21 ANSWER 4 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2003323839 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12853144
TITLE: BNF-1, a novel gene encoding a putative **extracellular matrix** protein, is **overexpressed** in tumor tissues.
AUTHOR: Wu Inmin; Moses Marsha A
CORPORATE SOURCE: Laboratory for Surgical Research, Children's Hospital, Harvard Medical School, Boston, MA 02115, USA.
CONTRACT NUMBER: P01 CA 45548 (NCI)
SOURCE: Gene, (2003 Jun 5) 311 105-10.
Journal code: 7706761. ISSN: 0378-1119.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AY163868
ENTRY MONTH: 200309
ENTRY DATE: Entered STN: 20030711
Last Updated on STN: 20030924
Entered Medline: 20030923

AB In an effort to identify novel genes relevant to tumor **angiogenesis**, we compared the genes **expressed** in a matched pair composed of **vascularized** breast tumor and its adjacent normal tissue obtained from the same cancer patient. Using **differential** display, we identified a cDNA fragment that was reproducibly upregulated in **vascularized** breast tumor. Up-regulation of this gene fragment in **vascularized** breast tumor was further verified by semi-quantitative PCR on the same RNA pair using gene-specific primers. The cDNA encoding the full-length ORF of that gene was then cloned by both 3' and 5' RACE. Sequence analysis showed that this gene encodes an ORF of 1353 bp having a hydrophobic N-terminal signal sequence and a cleavage site. We named this novel gene BNF-1 (breast tumor novel factor 1). The mature protein of this gene contains cysteine-rich repeats that are a specific feature of several **extracellular matrix** proteins including thrombospondin-1, **thrombospondin-2**, pro-collagen type 1, and von Willebrand Factor 1. PCR analysis of BNF-1 **expression** in a variety of **human** adult normal tissues revealed that BNF-1 is **expressed** predominantly in liver, heart, prostate, testis, and ovary. To further study the **expression** pattern of this novel gene in tumor tissues, we extended our analysis to additional matched pairs of tumor tissues obtained from breast, lung, and colon cancer patients. We show here that BNF-1 is over-**expressed** not only in breast tumors but also in lung and colon tumors.

L21 ANSWER 5 OF 36 MEDLINE on STN

ACCESSION NUMBER: 2003265979 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12792739
TITLE: **Overexpression** of the **thrombospondin 2** (**TSP2**) gene modulated by the **matrix** metalloproteinase family **expression** and production in **human** colon carcinoma **cell** line.
AUTHOR: Kamochi Junichiro; Tokunaga Tetsuji; Tomii Yasushi; Abe Yoshiyuki; Hatanaka Hiroyuki; Kijima Hiroshi; Yamazaki Hitoshi; Watanabe Norihito; Matsuzaki Shohei; Ueyama Yoshito; Nakamura Masato
CORPORATE SOURCE: Department of Pathology, Tokai University School of Medicine, Bohseidai, Isehara, Kanagawa 259-1143, Japan.
SOURCE: Oncology reports, (2003 Jul-Aug) 10 (4) 881-4.
Journal code: 9422756. ISSN: 1021-335X.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200402
ENTRY DATE: Entered STN: 20030608
Last Updated on STN: 20040207
Entered Medline: 20040206

AB **Thrombospondin 2** (**TSP2**) is an **extracellular matrix** glycoprotein involved in tumor progression and **angiogenesis.** We evaluated whether **overexpression** of the **TSP2** gene show an alteration of various genes by cDNA arrays in the colon carcinoma **cell** line SW480. The transformants with the **human TSP2** gene **overexpression** showed a down-regulation of **matrix** metalloproteinase 2 (MMP2) and MMP9 in comparison to those with vector-control. Protein production of MMP2 and MMP9 decreased in the transformants **overexpressing** the **TSP2** gene. Conversely, the SW480 transformants showed up-regulation of MMP12 and MMP17. These results suggested that the **TSP2** gene is a multifunctional modulator of remodeling tissue in which **matrix** degradation is required.

L21 ANSWER 6 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2003135370 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12605021
TITLE: Effects of cerivastatin on **human** arterial smooth muscle **cell** growth and **extracellular matrix expression** at varying glucose and low-density lipoprotein levels.
AUTHOR: Siegel-Axel Dorothea I; Runge Heike; Seipel Ludger; Riessen Reimer
CORPORATE SOURCE: Department of Medicine III, University of Tubingen, Germany.. daaxel@med.uni-Tuebingen.de
SOURCE: Journal of cardiovascular pharmacology, (2003 Mar) 41 (3) 422-33.
Journal code: 7902492. ISSN: 0160-2446.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030325
Last Updated on STN: 20031010
Entered Medline: 20031009

AB Statins exert pleiotropic effects on several other **cellular** functions besides lipid-lowering. Previously, it was found that cerivastatin is a very potent inhibitor of **human** arterial smooth muscle **cell** (haSMC) growth. However, because increased **extracellular matrix** (ECM) synthesis also accounts mainly for intimal plaque formation, the effects of cerivastatin on ECM **expression** was examined in this study. Furthermore, the influence of varying glucose and low-density lipoprotein (LDL) levels on cerivastatin-treated haSMCs was analyzed to mimic the conditions in patients with diabetes or hypercholesterolemia. The haSMCs were treated with 0.001-5.0 **microM** cerivastatin in the presence of 5.5-18.9 m glucose and 10-1000 **microg**/ml LDL. After 3 days, the messenger RNA (mRNA) **expression** of eight ECM proteins was analyzed and, after 7 days, mitotic and mitochondrial activities and thrombospondin (TSP)-1 protein **expression** were analyzed. TSP-1 and **TSP -2** mRNA **expression** was inhibited highly significantly at cerivastatin doses >or=0.01 **microM** with maximums of 72% and 35%, respectively, at high glucose levels. The mRNA signals of the third glycoprotein fibronectin were not influenced. Furthermore, collagen-1 mRNA was inhibited highly significantly up to 71% and biglycan mRNA was similarly inhibited up to 45%. The mRNA **expression** of the **matrix**-stimulating transforming growth factor (TGF)-beta1 and **matrix** metalloproteinase (MMP)-2 was not altered significantly, whereas mRNA **expression** of the tissue inhibitor of metalloproteinase (TIMP)-2 was stimulated clearly up to 150%. Mevalonate, but not LDL replacement, reversed the effects. Immunofluorescence staining showed an unaltered TSP-1 pattern with cerivastatin doses up to 0.1 **microM** whereas higher doses impaired TSP-1 excretion. The effects of cerivastatin on haSMC growth and mRNA **expression** of the eight ECM components were not diminished by the increase in LDL and glucose levels. Since accelerated SMC growth and ECM formation contribute mainly to intimal thickening, cerivastatin may be protective against the development of atherosclerotic and restenotic lesions by its direct **cellular** effects. Increased LDL and glucose levels, as in diabetes, do not mitigate the beneficial effects of cerivastatin on **cell** growth and ECM formation in vitro.

L21 ANSWER 7 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2003024662 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12531431
TITLE: Molecular mechanism of the anti-cancer activity of cerivastatin, an inhibitor of HMG-CoA reductase, on aggressive **human** breast cancer **cells.**
AUTHOR: Denoyelle Christophe; Albanese Patricia; Uzan Georges; Hong Li; Vannier Jean-Pierre; Soria Jeannette; Soria Claudine
CORPORATE SOURCE: Laboratoire DIFEMA, Groupe de Recherche MERCI, UFR de Medecine et de Pharmacie, 76183 Rouen, France.
SOURCE: Cellular signalling, (2003 Mar) 15 (3) 327-38. Journal code: 8904683. ISSN: 0898-6568.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030118
Last Updated on STN: 20030829
Entered Medline: 20030828

AB Statins are currently used for the treatment of hypercholesterolemia. Recently, we demonstrated that cerivastatin also reduces the proliferation and invasion of aggressive breast cancer **cells**, MDA-MB-231. In

this report, a molecular mechanism to explain its anti-cancer action is proposed by combining the study of cerivastatin effect on both gene **expression** (**microarray**) and signal transduction pathways. Firstly, the **expression** of 13 genes was modified by cerivastatin and confirmed at protein level. They could contribute to the inhibition of both **cell proliferation** (down-regulation of cyclin D1, PCNA, c-myc and up-regulation p21(Waf1), p19(INK4d), integrin beta8) and **cell** invasion, either directly (decrease in u-PA, MMP-9, u-PAR, PAI-1 and increase in anti-oncogenes Wnt-5a and H-cadherin) or indirectly by stimulating an anti-angiogenic gene (**thrombospondin**-2). The anti-angiogenic activity was confirmed by in vivo experiments. Secondly, we demonstrated that the biochemical mechanism of its anti-cancer action could be mainly explained by the inhibition of RhoA-dependent **cell** signalling. This hypothesis was supported by the fact that a RhoA inhibitor (C3 exoenzyme) or a dominant negative mutant RhoA (N19RhoA) induced similar effects to those of cerivastatin. In conclusion, cerivastatin, by preventing RhoA prenylation, inhibits (i) the RhoA/ROCK pathway, leading to defective actin stress **fibres** formation responsible for the loss of traction forces required for **cell** motility and (ii) the RhoA/FAK/AKT signalling pathway that could explain the majority of cancer-related gene modifications described above. Thus, the inhibition of RhoA **cell** signalling could be a good strategy in therapy of aggressive forms of breast cancer.

L21 ANSWER 8 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2002492414 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12353704
TITLE: **Differential expression** of **thrombospondin 2** in primary and metastatic malignant melanoma.
AUTHOR: Kunz M; Koczan D; Ibrahim S M; Gillitzer R; Gross G; Thiesen H J
CORPORATE SOURCE: Department of Dermatology and Venereology, University of Rostock, Germany.. manfred.kunz@med.uni-rostock.de
SOURCE: Acta dermato-venereologica, (2002) 82 (3) 163-9. Journal code: 0370310. ISSN: 0001-5555.
PUB. COUNTRY: Norway
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20021001
Last Updated on STN: 20030214
Entered Medline: 20030213

AB In the present report we used oligonucleotide **microarray** analysis for the identification of genes characterizing the late-stage metastatic phenotype of malignant melanoma. A panel of 5,600 genes was analysed in a low aggressive and a highly aggressive (metastatic) **human** malignant melanoma **cell** line, respectively. More than 300 **differentially** regulated genes were identified. High metastatic potential correlated with upregulated mRNA **expression** in the groups of cytoskeletal proteins, apoptosis and **cell** cycle proteins, GTP binding proteins and oncogenes, **extracellular** ligands and receptors, transcription and translation factors. In contrast, most **angiogenesis** factors, **extracellular** **matrix** molecules, and melanoma-specific antigens were downregulated. Particular target genes were further analysed by in situ hybridization and immunohistochemical staining of primary malignant

melanomas and melanoma metastases. Here, we show that **thrombospondin 2**, an **extracellular matrix** molecule which was **differentially** regulated in the **microarray** analysis, was strongly **expressed** in melanoma metastases, but not in primary tumours. The identification of **thrombospondin 2** as a target molecule emphasizes the importance of **cell-matrix** interactions for the pathogenesis of malignant melanoma metastasis and may open future perspectives for treatment of this tumour.

L21 ANSWER 9 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2002315748 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12058057
TITLE: **Thrombospondin 2** inhibits **microvascular** endothelial **cell proliferation** by a caspase-independent mechanism.
AUTHOR: Armstrong Lucas C; Bjorkblom Benny; Hankenson Kurt D; Siadak Anthony W; Stiles Charlotte E; Bornstein Paul
CORPORATE SOURCE: Department of Biochemistry, University of Washington, Seattle, Washington 98195, USA.
CONTRACT NUMBER: AR-45418 (NIAMS)
DE-07063 (NIDCR)
HL-18645 (NHLBI)
RR0161 (NCRR)
SOURCE: Molecular biology of the cell, (2002 Jun) 13 (6) 1893-905. Journal code: 9201390. ISSN: 1059-1524.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20020612
Last Updated on STN: 20021218
Entered Medline: 20021213

AB The **matricellular** protein **thrombospondin 2** (**TSP2**) regulates a variety of **cell-matrix** interactions. A prominent feature of **TSP2**-null mice is increased **microvascular** density, particularly in connective tissues synthesized after injury. We investigated the **cellular** basis for the regulation of **angiogenesis** by **TSP2** in cultures of murine and **human fibroblasts** and endothelial **cells**. **Fibroblasts** isolated from murine and **human** dermis synthesize **TSP2** mRNA and secrete significant amounts of immunoreactive **TSP2**, whereas endothelial **cells** from mouse lung and **human** dermis did not synthesize **TSP2** mRNA or protein. Recombinant mouse **TSP2** inhibited growth of **human microvascular** endothelial **cells** (HMVECs) mediated by basic **fibroblast** growth factor, insulin-like growth factor-1, epidermal growth factor, and **vascular** endothelial growth factor (VEGF). HMVECs exposed to **TSP2** in the presence of these growth factors had a decreased proportion of **cells** in S and G2/M phases. HMVECs cultured with a combination of basic **fibroblast** growth factor, insulin-like growth factor-1, and epidermal growth factor displayed an increased proportion of nonviable **cells** in the presence of **TSP2**, but the addition of VEGF blocked this **TSP2**-mediated impairment of **cell** viability. **TSP2**-mediated inhibition of DNA synthesis by HMVECs in the presence of VEGF was not affected by the broad-spectrum caspase inhibitor zVAD-fmk. Similar findings were obtained with TSP1. Taken together, these observations indicate that either

TSP2 or TSP1 can inhibit HMVEC **proliferation** by inhibition of **cell** cycle progression and induction of **cell** death, but the mechanisms responsible for **TSP2**-mediated inhibition of **cell** cycle progression are independent from those leading to **cell** death.

L21 ANSWER 10 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2002196761 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11929817
TITLE: **Systemic** inhibition of tumor growth and **angiogenesis** by **thrombospondin-2** using **cell**-based antiangiogenic gene therapy.
AUTHOR: Streit Michael; Stephen Antonia E; Hawighorst Thomas; Matsuda Kant; Lange-Asschenfeldt Bernhard; Brown Lawrence F; Vacanti Joseph P; Detmar Michael
CORPORATE SOURCE: Cutaneous Biology Research Center and Department of Dermatology, Massachusetts General Hospital and Harvard Medical School, Charlestown 02129, USA.
CONTRACT NUMBER: CA 69184 (NCI)
CA 86410 (NCI)
CA71345-04 (NCI)
SOURCE: Cancer research, (2002 Apr 1) 62 (7) 2004-12.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020404
Last Updated on STN: 20020508
Entered Medline: 20020507
AB Recent studies indicate that continuous administration improves the **antitumoral** efficacy of **angiogenesis** inhibitors, as compared with intermittent dosing, suggesting a potential role of gene therapy in antiangiogenic tumor therapy. We established a tissue-engineered **implant system** for the continuous in vivo production of **thrombospondin-2** (**TSP-2**), a potent endogenous inhibitor of tumor growth and **angiogenesis**. **Fibroblasts** were retrovirally transduced to **overexpress TSP-2** and were seeded onto biodegradable **polymer** scaffolds. After transplantation into the peritoneal cavity of nude mice, **bioimplants** maintained high levels of **TSP-2** secretion over extended time periods, resulting in increased levels of circulating **TSP-2**. **Bioimplant**-generated **TSP-2** potently inhibited tumor growth and **angiogenesis** of **human** squamous **cell** carcinomas, malignant melanomas, and Lewis lung carcinomas that were **implanted** at a distant site. These results provide the first proof-of-principle for the feasibility and therapeutic efficiency of **systemic**, **cell**-based antiangiogenic gene therapy using biodegradable **polymer grafts** for the treatment of cancer.

L21 ANSWER 11 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2001516232 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11563036
TITLE: Antisense oligonucleotide ISIS 2922 targets IE-**expression** and prevents HCMV-IE-induced suppression of TSP-1 and **TSP-2 expression**

AUTHOR: Margraf S; Bittoova M; Vogel J U; Kotchekov R; Doerr H W; Cinatl J Jr
CORPORATE SOURCE: J. W. Goethe University Hospital, Inst. f. Med. Virology, Paul Ehrlich-Str. 40, D-60596 Frankfurt am Main, Germany.
SOURCE: Nucleosides, nucleotides & nucleic acids, (2001 Apr-Jul) 20 (4-7) 1425-8.
Journal code: 100892832. ISSN: 1525-7770.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20010924
Last Updated on STN: 20020125
Entered Medline: 20020109

AB ISIS 2922, but not ganciclovir (GCV), inhibits HCMV immediate early protein (IE) **expression** in **different infected cell** lines and prevents down-modulation of **extracellular matrix** proteins thrombospondin-1 and -2 induced by IE proteins. While action of ISIS 2922 is mainly due to specific inhibition of IE 2 mRNA, there is also evidence for unspecific effects in terms of inhibition of virus adhesion and penetration.

L21 ANSWER 12 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2001488077 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11530335
TITLE: Thrombospondins and tumor **angiogenesis.**
AUTHOR: de Fraipont F; Nicholson A C; Feige J J; Van Meir E G
CORPORATE SOURCE: INSERM EMI 0105, Dept of Molecular and Structural Biology, Commissariat a l'Energie Atomique, Grenoble, France.
CONTRACT NUMBER: CA86335 (NCI)
NS 41403 (NINDS)
T32 NS07480 (NINDS)
SOURCE: Trends in molecular medicine, (2001 Sep) 7 (9) 401-7. Ref: 75
Journal code: 100966035. ISSN: 1471-4914.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200111
ENTRY DATE: Entered STN: 20010903
Last Updated on STN: 20011105
Entered Medline: 20011101

AB The thrombospondins (TSPs) are a family of five secreted proteins that are widely distributed in the **extracellular matrix** of numerous tissues. TSPs are multimodular and each domain specifies a distinct biological function through interaction with a specific receptor. TSP1 and **TSP2** have anti-angiogenic activity, which, at least for TSP1, involves interaction with the **microvascular** endothelial **cell** receptor CD36. **Expression** of TSP1 and **TSP2** is modulated by hypoxia and by oncogenes. In several tumors (thyroid, colon, bladder carcinomas), TSP1 **expression** is inversely correlated with tumor grade and survival rate, whereas in others (e.g. breast carcinomas), it is correlated with the stromal response and is of little prognostic value. Recent studies suggest that TSPs or TSP-derived peptides retaining biological activity could be developed into promising new therapeutic strategies for the anti-angiogenic treatment of solid

tumors.

L21 ANSWER 13 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2001325292 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11306593
TITLE: Thrombospondins as **matricellular** modulators of **cell** function.
AUTHOR: Bornstein P
CORPORATE SOURCE: Departments of Biochemistry and Medicine, University of Washington, Seattle, WA 98195, USA.. bornsten@u.washington.edu
CONTRACT NUMBER: AR-45418 (NIAMS)
HL-18645 (NHLBI)
SOURCE: Journal of clinical investigation, (2001 Apr) 107 (8) 929-34. Ref: 38
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010611
Last Updated on STN: 20010611
Entered Medline: 20010607

L21 ANSWER 14 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2001138929 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11102746
TITLE: **Thrombospondin 2**, a **matricellular** protein with diverse functions.
AUTHOR: Bornstein P; Armstrong L C; Hankenson K D; Kyriakides T R; Yang Z
CORPORATE SOURCE: Department of Biochemistry, University of Washington, Seattle, WA 98195, USA.. bornsten@u.washington.edu
CONTRACT NUMBER: AR 45418 (NIAMS)
DE 07063 (NIDCR)
HL 18645 (NHLBI)
SOURCE: Matrix biology : journal of the International Society for Matrix Biology, (2000 Dec) 19 (7) 557-68. Ref: 77
Journal code: 9432592. ISSN: 0945-053X.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010308
AB Thrombospondin (**TSP**) **2** is a close relative of TSP1 but differs in its temporal and spatial distribution in the mouse. This difference in **expression** undoubtedly reflects the marked disparity in the DNA sequences of the promoters in the genes encoding the two proteins. The synthesis of **TSP2** occurs primarily in connective tissues of the developing and growing mouse. In the adult animal the protein is again produced in response to tissue injury and in association with the growth of tumors. Despite the abnormalities in

collagen fibrillogenesis, fragility of skin, and laxity of tendons and ligaments observed in the **TSP2**-null mouse, **TSP2** does not appear to contribute directly to the structural integrity of connective tissue elements. Instead, emerging evidence supports a mode of action of **TSP2** 'at a distance', i.e. by modulating the activity and bioavailability of proteases and growth factors in the **pericellular** environment and, very likely, by interaction with **cell**-surface receptors. Thus, **TSP2** qualifies as a **matricellular** protein, as defined in the introduction to this minireview series. The phenotype of **TSP2**-null mice has been very helpful in providing clues to the functions of **TSP2.** In addition to histological and functional abnormalities in connective tissues, these mice display an increased **vascularity** of the dermis and subdermal tissues, increased endosteal bone growth, a bleeding defect, and a marked adhesive defect of dermal **fibroblasts.** Our laboratory has established that **TSP2** binds **matrix** metalloproteinase 2 (MMP2) and that the adhesive defect in **TSP2** -null **fibroblasts** results from increased MMP2 activity. The investigation of the basis for the other defects in the **TSP2** -null mouse is likely to yield equally interesting results.

L21 ANSWER 15 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2001138026 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11147677
TITLE: **Thrombospondin 2** modulates collagen fibrillogenesis and **angiogenesis.**
AUTHOR: Bornstein P; Kyriakides T R; Yang Z; Armstrong L C; Birk D E
CORPORATE SOURCE: Department of Biochemistry, University of Washington, Seattle 98195, USA.. bornsten@u.washington.edu
CONTRACT NUMBER: AR44745 (NIAMS)
AR45418 (NIAMS)
HL18645 (NHLBI)
SOURCE: journal of investigative dermatology. Symposium proceedings / the Society for Investigative Dermatology, Inc. [and] European Society for Dermatological Research, (2000 Dec) 5 (1) 61-6. Ref: 28
Journal code: 9609059. ISSN: 1087-0024.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010308

AB **Thrombospondin 2** (**TSP2**)-null mice, generated by targeted disruption of the Thbs2 gene, display a complex phenotype that is characterized, in part, by a variety of connective tissue abnormalities and increased **vascular** density in skin and subcutaneous tissues. In this paper we summarize the evidence that **TSP2** functions as a **matricellular** protein to influence **cell** function by modulating **cell-matrix** interactions, rather than acting as an integral component of the **matrix.** Thus, the structurally abnormal collagen fibrils detected in skin appear to be the consequence of the defective adhesion demonstrated by dermal **fibroblasts** in culture that, in turn, result from increased **matrix** metalloproteinase 2 (MMP2, gelatinase A) production by

these **cells**. Corroborating evidence for such a mode of action comes from transmission electron **microscopic** images of developing flexor muscle tendons that show distinct abnormalities in **fibroblast**-collagen fibril interactions in **TSP2**-null tissue. The increased **vascular** density seen in skin of **TSP2**-null mice can be reproduced in a number of models of injury, including subcutaneous **implantation** of polyvinyl alcohol sponges and silicone rubber discs, and excisional skin wounds. Experiments are proposed to distinguish between a primarily endothelial **cell** versus an **extracellular matrix** origin for the increased **angiogenesis** in **TSP2**-null mice.

L21 ANSWER 16 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2001021516 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10950755
TITLE: Cytomegalovirus **infection** decreases **expression** of thrombospondin-1 and -2 in cultured **human** retinal glial **cells**: effects of antiviral agents.
AUTHOR: Cinatl J Jr; Bittoova M; Margraf S; Vogel J U; Cinatl J; Preiser W; Doerr H W
CORPORATE SOURCE: Institut fur Medizinische Virologie, Zentrum der Hygiene, Klinikum der Johann Wolfgang Goethe-Universitat, D-60596 Frankfurt am Main, Germany.. cinatl@em.uni-frankfurt.de
SOURCE: Journal of infectious diseases, (2000 Sep) 182 (3) 643-51. Journal code: 0413675. ISSN: 0022-1899.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20030105
Entered Medline: 20001103

AB In **fibroblasts**, **infection** with **human** cytomegalovirus (HCMV) inhibits **expression** of the **extracellular matrix** proteins thrombospondin-1 and -2 (TSP-1 and **TSP-2**). These effects may depend on **expression** of HCMV immediate-early (IE) genes, which are activated by **cellular** transcription factor NF-kappaB. The influence of HCMV **infection** on TSP-1 and **TSP-2** **expression** and the ability of **different** antiviral drugs to prevent these **cellular** changes in permissive cultures of **human** retinal glial **cells** were observed. Ganciclovir inhibited only HCMV late antigen (LA) **expression**, whereas antisense oligonucleotide ISIS 2922 and peptide SN50, inhibitors of HCMV IE **expression** and NF-kappaB activity, respectively, inhibited both IE and LA **expression.** ISIS 2922 and SN50, but not ganciclovir, prevented down-modulation of TSP-1 and **TSP-2.** The results showed that HCMV-induced down-modulation of TSP-1 and **TSP-2** in retinal glial **cells** is prevented by inhibition of HCMV IE **expression.** These findings may be relevant to pathogenesis and treatment of HCMV retinitis.

L21 ANSWER 17 OF 36 MEDLINE on STN
ACCESSION NUMBER: 1999300995 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10372407
TITLE: [Thrombospondins, tumor **angiogenesis** and breast cancer].
Thrombospondines, angiogenese tumorale et cancer du sein.

AUTHOR: Clezardin P; Bruno-Bossio G; Fontana A; Serre C M; Magnetto S; Frappart L
CORPORATE SOURCE: INSERM Unite 403, Faculte de Medecine Laennec, Lyon, France.
SOURCE: Pathologie-biologie, (1999 Apr) 47 (4) 368-74. Ref: 39
Journal code: 0265365. ISSN: 0369-8114.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990820
Last Updated on STN: 19990820
Entered Medline: 19990806

AB Thrombospondin-1 and -2 are **extracellular matrix** proteins that are **overexpressed** in breast cancer tissue. Their role in breast cancer remains unknown. This article reviews the potential effects of thrombospondin-1 and -2 in breast cancer tumori genesis and metastatic dissemination.

L21 ANSWER 18 OF 36 MEDLINE on STN
ACCESSION NUMBER: 1999300990 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10372402
TITLE: [Thrombospondins: multimodular proteins with angiostatic function].
Thrombospondines: des proteines multimodulaires a fonction angiostatique.
AUTHOR: Feige J J
CORPORATE SOURCE: Unite INSERM 244, Departement de Biologie Moleculaire et Structurale, Grenoble, France.
SOURCE: Pathologie-biologie, (1999 Apr) 47 (4) 339-44. Ref: 33
Journal code: 0265365. ISSN: 0369-8114.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990820
Last Updated on STN: 19990820
Entered Medline: 19990806

AB The thrombospondins (TSPs) are a family of multimodular proteins that bind to the **extracellular matrix** with strong affinity. Of the five members of the TSP family, TSP1 and **TSP2** are the only ones that inhibit endothelial **cell** migration in vitro and **neoangiogenesis** in vivo. This **angiogenesis**-inhibiting effect is mediated by interaction of a short sequence in type I modules with the membrane receptor CD36. TSP1 and **TSP2** gene knockout experiments in mice showed increased **blood vessel** density in **TSP2** -/- but no such alteration in TSP1 -/- animals. Loss of TSP1 gene **expression** was correlated with acquisition of an angiogenic phenotype in several models of **human** malignant tumors. Taken in concert, these findings suggest that TSP1 and, to a lesser extent, **TSP2** may have therapeutic potential as **angiogenesis**-inhibiting factors.

L21 ANSWER 19 OF 36 MEDLINE on STN

ACCESSION NUMBER: 1999054177 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9840442
TITLE: Two-hybrid analysis reveals multiple direct interactions for thrombospondin 1.
AUTHOR: Aho S; Uitto J
CORPORATE SOURCE: Department of Dermatology and Cutaneous Biology, Jefferson Medical College, and the Jefferson Institute of Molecular Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania 19107-5541, USA.
CONTRACT NUMBER: PO1-AR38923 (NIAMS)
SOURCE: Matrix biology : journal of the International Society for Matrix Biology, (1998 Oct) 17 (6) 401-12.
Journal code: 9432592. ISSN: 0945-053X.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990216
Last Updated on STN: 19990216
Entered Medline: 19990202

AB The yeast two-hybrid **system** was used to reveal the interactions between proteins residing within the cutaneous basement membrane zone and other gene products **expressed** in cultured **human** keratinocytes. The proteins of interest included type VII collagen, the predominant component of anchoring fibrils, and laminin 5, a component of anchoring filaments. Although the two-hybrid **system** was not able to verify a direct interaction between the type VII collagen NC1 domain and the short arm of Lam(beta)3, the type VII collagen NC1 domain (tVII/NC1) and the laminin 5 beta3 chain globular domain VI (lam5/beta3) cDNAs, when used as baits, detected four overlapping cDNA clones encoding thrombospondin 1 (TSP1). The overlapping region of these cDNAs encodes amino acids 400-459, a segment included within a 70 kDa chymotryptic fragment known to bind type V collagen, laminin-1 and other **matrix** components. The type VII collagen NC1/TSP1 interaction was confirmed by exchanging the vectors, and the interacting domain was mapped by testing a set of both 5' and 3' deletion constructs. The central region of TSP1, when used as a bait in two-hybrid **system**, showed strong binding to the fibronectin (FN) type III-like repeats 4-7 of type VII collagen NC1 domain. The TSP1 bait also interacted with laminin 5 beta3 chain domain V/III, and the TSP1/laminin 5 beta3 chain interaction was verified by a GST-fusion protein interaction assay. The transcripts encoding TSP1, **TSP2**, Lam(beta)3 and type VII collagen were abundant in cultured foreskin keratinocytes, and the **expression** of TSP1 and **TSP2** in a wide variety of adult and fetal tissues was confirmed by PCR analysis of multiple tissue cDNA panels. Furthermore, TSP1 type I repeats showed self interaction, and recognized a clone for **extracellular matrix** protein fibrillin-2. In addition, clones encoding **angiogenesis** related protein Jagged1 and a platelet enzyme phospholipase scramblase were identified. Thus, the results indicate several previously undetected interactions of TSP1, which is known to be highly **expressed** during embryonic development, tissue remodeling and wound healing.

L21 ANSWER 20 OF 36 MEDLINE on STN
ACCESSION NUMBER: 1998357946 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9694573
TITLE: Hormonally regulated components of the adrenocortical **cell** environment and the control of adrenal cortex homeostasis.

AUTHOR: Feige J J; Keramidas M; Chambaz E M
CORPORATE SOURCE: INSERM Unite 244, Departement de Biologie Moleculaire et Structurale, CEA Grenoble, France..
jjfeige@geant.ceng.cea.fr
SOURCE: Hormone and metabolic research. Hormon- und Stoffwechselforschung. Hormones et metabolisme, (1998 Jun-Jul) 30 (6-7) 421-5. Ref: 42
Journal code: 0177722. ISSN: 0018-5043.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981021
Last Updated on STN: 19981021
Entered Medline: 19981013

AB The **extracellular matrix** (ECM) strongly contributes to the regulation of **cell proliferation** and **cell differentiation**, and thereby of embryonic development and adult tissue homeostasis. We review here the ongoing characterization of the structure and functions of the **extracellular matrix** components secreted by adrenocortical **cells** and discuss their possible implication in the hormonal regulation of adrenal cortex homeostasis. Fibronectin (FN) and laminin (LN) are both major adhesive proteins for adrenocortical **cells.** FN is synthesized by bovine fasciculata **cells** in primary culture, and its synthesis is stimulated by TGF(beta)1, TGF(beta)2, and FGF-2 but is not modified by IGF-1 or by the hormones ACTH and angiotensin II. LN is also synthesized by bovine fasciculata **cells** and its synthesis is specifically stimulated by ACTH. Both proteins are haptotactic and chemotactic for adrenocortical **cells**, suggesting a physiological role in adrenocyte migration. Their distribution in the adrenal gland is quite distinct. LN is uniformly present in the steroidogenic **cells** from the three zones, whereas FN is abundant in the **fibrovascular** structures of the capsule and the cortex. ACTH treatment of adrenocortical **cells** strongly induces the **expression** and secretion of **thrombospondin-2** (**TSP2**), a large trimeric **matricellular** protein. The multimodular structure of **TSP2** is the support of a variety of biological functions. **TSP2** promotes attachment but prevents spreading of adrenocortical **cells.** On the other hand, **TSP2** induces the activation of latent TGFbeta through an indirect mechanism and is anti-angiogenic in vitro. The overall distribution of **TSP2** in the glomerulosa and fasciculata zones of the adrenal cortex, and its absence from the reticularis zone, argue in favor of a role in the protection of adrenocortical **cells** against apoptosis. In the adrenal cortex, five main biological functions are potentially regulated by components of the **extracellular matrix** : **stem cell** commitment into the adrenocyte **differentiation** pathway, terminal **differentiation** toward the three distinct adrenocyte phenotypes, centripetal migration, apoptosis and the formation of the capillary network. Future studies will aim at deciphering which **extracellular** component(s) is involved in each of these regulations.

L21 ANSWER 21 OF 36 MEDLINE on STN
ACCESSION NUMBER: 97164656 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9012463

TITLE: Thrombospondin-1 and -2 messenger RNA **expression** in normal, benign, and neoplastic **human** breast tissues: correlation with prognostic factors, tumor **angiogenesis**, and **fibroblastic** desmoplasia.
AUTHOR: Bertin N; Clezardin P; Kubiak R; Frappart L
CORPORATE SOURCE: Department of Pathology and CNRS UMR 5641, Edouard Herriot Hospital, Lyon, France.
SOURCE: Cancer research, (1997 Feb 1) 57 (3) 396-9.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970305
Last Updated on STN: 19980206
Entered Medline: 19970220

AB Thrombospondin-1 (TSP1) is a Mr 450,000 **extracellular matrix** glycoprotein that modulates tumor growth, **angiogenesis**, and metastasis. Of the five structurally **different** TSPs described to date, only **TSP2** is similar to TSP1 in terms of its molecular architecture, and **TSP2** also modulates **angiogenesis. Angiogenesis** plays a relevant role in the biological aggressiveness of breast cancer, and TSP1 is present in the tumor stroma (termed desmoplasia) of invasive **human** breast ductal carcinoma not otherwise specified (NOS). The present study was designed to identify and quantify TSP1 and **TSP2** mRNAs in normal, benign, and neoplastic **human** breast tissues using the reverse transcriptase PCR technique. We found that **TSP2**, like TSP1, was **expressed** in **human** breast tissues, and that TSP1 and **TSP2** mRNA **expression** in invasive breast carcinoma NOS was significantly increased compared to that observed in normal and benign tissues. The **expression** of TSP1 and **TSP2** in invasive breast ductal carcinoma NOS did not significantly correlate with any of the prognostic factors studied (tumor size, lymph node status, morphology, and hormone receptor status). However, when our study population was divided according to the quantity of tumor stroma, TSP1 (and possibly **TSP2**) mRNA **expression** and **microvessel** counts in desmoplastic-rich stroma of breast carcinoma NOS were significantly increased compared to those observed in desmoplastic-poor stromata.

L21 ANSWER 22 OF 36 MEDLINE on STN
ACCESSION NUMBER: 93216653 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8463250
TITLE: Thrombospondin is a tight-binding competitive inhibitor of neutrophil elastase.
AUTHOR: Hogg P J; Owensby D A; Mosher D F; Misenheimer T M; Chesterman C N
CORPORATE SOURCE: Centre for Thrombosis and Vascular Research, Prince of Wales Hospital, University of New South Wales, Sydney, Australia.
CONTRACT NUMBER: HL29586 (NHLBI)
SOURCE: Journal of biological chemistry, (1993 Apr 5) 268 (10) 7139-46.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199305
ENTRY DATE: Entered STN: 19930521
Last Updated on STN: 20000303
Entered Medline: 19930505

AB Thrombospondin, a glycoprotein of three identical disulfide-bonded subunits, is a constituent of platelet alpha-granules and a variety of normal and transformed **cells** and binds to **cell** surfaces and becomes incorporated into **extracellular matrix.** It has been implicated in processes such as wound healing and tumor growth and metastasis. In addition, thrombospondin was shown recently to be an inhibitor of the fibrinolytic enzyme, plasmin. In the cause of studying the effects of thrombospondin on other serine proteinases, we found that thrombospondin binds neutrophil elastase in an active-site-dependent manner and competitively inhibits the activity of the enzyme. In a competitive binding assay, neutrophil elastase bound to thrombospondin with a dissociation constant of 17 +/- 7 nM, **expressed** per mole of thrombospondin trimer, or 52 +/- 20 nM, **expressed** per mole of thrombospondin subunit. In kinetic studies of the inhibition of the amidolytic activity of neutrophil elastase by **thrombospondin**, 2.7 +/- 0.3 mol of elastase interacted with 1 mol of thrombospondin trimer with a site-binding constant of 57 +/- 13 nM. Lower limits for the on rate constant of 5 x 10(6) M-1 s-1 and off rate constant of 0.27 s-1 were established. Affinity of binding of neutrophil elastase to thrombospondin was sensitive to ionic strength and calcium ions. Thrombospondin was cleaved by neutrophil elastase, but the site(s) of the limited cleavage are independent of the competitive inhibition of elastase activity by thrombospondin. Neutrophil elastase inactivated with phenylmethylsulfonyl fluoride did not compete with active elastase for binding to thrombospondin, implying that a functional active site is important for the interaction of elastase with thrombospondin. Thrombospondin protected fibronectin from cleavage by neutrophil elastase. In summary, the binding of neutrophil elastase to thrombospondin is tight, reversible, and close enough to the active site of elastase to exclude small synthetic tripeptidyl p-nitroanilide **substrates** and macromolecular protein **substrates.** Two potential reactive centers that may be involved in binding elastase have been identified in the calcium-binding type 3 domains of thrombospondin. Neutrophil elastase is the enzyme primarily responsible for degrading and solubilizing connective tissue during **inflammatory** processes. These findings suggest a previously unsuspected mechanism for regulation of elastase activity at **inflammatory** sites.

L21 ANSWER 23 OF 36 MEDLINE on STN
ACCESSION NUMBER: 92147683 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1371115
TITLE: Characterization of mouse **thrombospondin 2** sequence and **expression** during **cell** growth and development.
AUTHOR: Laherty C D; O'Rourke K; Wolf F W; Katz R; Seldin M F; Dixit V M
CORPORATE SOURCE: Department of Pathology, University of Michigan Medical School, Ann Arbor 48109.
CONTRACT NUMBER: DE-00301-01 (NIDCR)
HG-00101 (NHGRI)
HL-39037 (NHLBI)
SOURCE: Journal of biological chemistry, (1992 Feb 15) 267 (5) 3274-81.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-D12753; GENBANK-L07803; GENBANK-M84123; GENBANK-M84124; GENBANK-M84125; GENBANK-M84126; GENBANK-M84127; GENBANK-M84128; GENBANK-M84129; GENBANK-M84130
ENTRY MONTH: 199203
ENTRY DATE: Entered STN: 19920405
Last Updated on STN: 20000303
Entered Medline: 19920317

AB Thrombospondin (TSP) is an **extracellular matrix** glycoprotein whose **expression** has been associated with a variety of **cellular** processes including growth and embryogenesis. The recent discovery of the existence of a second mouse TSP gene necessitates careful examination of the discrete biochemical and functional properties associated with each molecule. In this report, the primary structures of **human** TSP, mouse TSP1 (mTSP1), mouse **TSP2** (mTSP2), and chicken TSP are compared; and the **expression** of mTSP1 and mTSP2 during embryogenesis and growth factor-mediated **cell proliferation** is examined. The cloning and sequencing of the entire coding regions of mTSP1 and mTSP2 revealed considerable conservation of residues critical for TSP structure and function; these data suggest that **TSP2** is capable of trimer formation and many of the same **cell**-surface and ligand interactions that mediate TSP function. Comparison of the various TSP sequences also allowed the assignment based on sequence homology of previously reported **human** TSP as TSP1 and chicken TSP as **TSP2.** mTSP2, like mTSP1, was shown to be a primary response gene when quiescent Swiss 3T3 **cells** were stimulated with serum, platelet-derived growth factor BB, basic **fibroblast** growth factor, or interleukin-1 beta. Interestingly, TSP1 and **TSP2** exhibited markedly **different** tissue- and stage-specific patterns of mRNA **expression** during mouse embryogenesis, implying that the two TSP molecules possess discrete functional properties important for development. Additionally, the TSP genes (Thbs1 and Thbs2) were mapped to single loci on mouse chromosomes 2 and 17, respectively.

L21 ANSWER 24 OF 36 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 2005:17202 BIOSIS
DOCUMENT NUMBER: PREV200500015595
TITLE: **Matricellular** proteins in the heart: possible role during stress and remodeling.
AUTHOR(S): Schellings, Mark W. M.; Pinto, Yigal M.; Heymans, Stephane [Reprint Author]
CORPORATE SOURCE: Dept CardiolCARIM, Univ Maastricht, P Debyelaan 25 POB 5800, NL-6202 AZ, Maastricht, Netherlands s.heymans@cardio.unimaas.nl
SOURCE: Cardiovascular Research, (October 1 2004) Vol. 64, No. 1, pp. 24-31. print.
CODEN: CVREAU. ISSN: 0008-6363.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Dec 2004
Last Updated on STN: 22 Dec 2004

AB **Matricellular** proteins are **extracellular matrix** proteins that modulate **cell-matrix** interactions and **cell** function, and do not seem to have a direct

structural role. The family includes tenascin-C (TN-C), tenascin-X (TN-X), osteonectin, osteopontin, thrombospondin-1 (TSPI) and **thrombospondin-2 (TSP2)**. **Expression** of **matricellular** proteins is high during embryogenesis, but almost absent during normal postnatal life. Interestingly, it re-appears in response to injury. Left ventricular remodeling is a complicated process that occurs in the stressed heart, and is still not completely understood. Several members of the **matricellular** protein family, like tenascin-C, osteopontin, and osteonectin are up-regulated after cardiac injury. Therefore, this group of proteins may have crucial functions in the heart coping with stress. This review will focus on the **expression**, regulation and function of these **matricellular** proteins, and will discuss the crucial functions that these proteins might exert during remodeling of the stressed heart.

L21 ANSWER 25 OF 36 BIOSIS on STN

ACCESSION NUMBER: 2005:583 BIOSIS
DOCUMENT NUMBER: PREV200500000106
TITLE: **Thrombospondin-2** is essential for myocardial **matrix** integrity - Increased **expression** identifies failure-prone cardiac hypertrophy.
AUTHOR(S): Schroen, Blanche; Heymans, Stephane; Sharma, Umesh; Blankesteijn, W. Matthijs; Pokharel, Saraswati; Cleutjens, Jack P. M.; Porter, J. Gordon; Evelo, Chris T. A.; Duisters, Rudy; van Leeuwen, Rick E. W.; Janssen, Ben J. A.; Debets, Jacques J. M.; Smits, Jos F. M.; Daemen, Mat J. A. P.; Crijns, Harry J. G. M.; Bornstein, Paul; Pinto, Yigal M. [Reprint Author]
CORPORATE SOURCE: Dept Cardiol, Univ Hosp Maastricht, NL-6202 AZ, Maastricht, Netherlands
Y.Pinto@cardio.azm.nl
SOURCE: Circulation Research, (September 3 2004) Vol. 95, No. 5, pp. 515-522. print.
ISSN: 0009-7330 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Dec 2004
Last Updated on STN: 16 Dec 2004

AB Cardiac hypertrophy can lead to heart failure (HF), but it is unpredictable which hypertrophied myocardium will progress to HF. We surmised that apart from hypertrophy-related genes, failure-related genes are **expressed** before the onset of failure, permitting molecular prediction of HF. Hearts from hypertensive homozygous renin-**overexpressing** (Ren-2) rats that had progressed to early HF were compared by **microarray** analysis to Ren-2 rats that had remained compensated. To identify which HF-related genes preceded failure, cardiac biopsy specimens were taken during compensated hypertrophy and we then monitored whether the rat progressed to HF or remained compensated. Among 48 genes **overexpressed** in failing hearts, we focused on **thrombospondin-2 (TSP2)**. **TSP2** was selectively **overexpressed** only in biopsy specimens from rats that later progressed to HF. Moreover, **expression** of **TSP2** was increased in **human** hypertrophied hearts with decreased (0.19+/-0.01) versus normal ejection fraction (0.11+/-0.03 (arbitrary units); P0.05). Angiotensin II induced fatal cardiac rupture in 70% of **TSP2** knockout mice, with cardiac failure in the surviving mice; this was not seen in wild-type mice. In **TSP2**

knockout mice, angiotensin II increased **matrix** metalloproteinase (MMP)-2 and MMP-9 activity by 120% and 390% compared with wild-type mice (P0.05). In conclusion, we identify **TSP2** as a crucial regulator of the integrity of the cardiac **matrix** that is necessary for the myocardium to cope with increased loading and that may function by its regulation of MMP activity. This suggests that **expression** of **TSP2** marks an early-stage molecular program that is activated uniquely in hypertrophied hearts that are prone to fail.

L21 ANSWER 26 OF 36 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:221301 BIOSIS
DOCUMENT NUMBER: PREV200400224378
TITLE: Stimulation of **angiogenesis** by Ras proteins.
AUTHOR(S): Kranenburg, Onno [Reprint Author]; Gebbink, Martijn F. B. G.; Voest, Emile E.
CORPORATE SOURCE: Department of Medical Oncology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, Netherlands o.kranenburg@azu.nl
SOURCE: Biochimica et Biophysica Acta, (4 March 2004) Vol. 1654, No. 1, pp. 23-37. print.
ISSN: 0006-3002 (ISSN print).
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Apr 2004
Last Updated on STN: 21 Apr 2004

AB **Cells** that have acquired a **proliferative** advantage form islets of hyperplasia during the initial stages of tumor development. Like normal **cells**, they require oxygen and nutrients to survive and proliferate. The centre of the islets is characterized by low oxygen pressure and low pH, conditions that stimulate the sprouting of new capillaries from nearby **vascular** beds. It is now well established that **neovascularisation** (**angiogenesis**) of the hyperplasias is essential for further development of the tumor. The family of ras oncogenes promotes the initiation of tumor growth by stimulating tumor **cell proliferation**, but also ensures tumor progression by stimulating tumor-associated **angiogenesis.** Oncogenic Ras proteins stimulate a number of effector pathways that culminate in the transcriptional activation of genes that control **angiogenesis.** Moreover, Ras signaling leads to stabilization of the produced mRNAs and, possibly, to enhanced initiation of their translation. In this review we describe the mechanisms that underlie Ras regulation of **vascular** endothelial growth factor (VEGF), cyclooxygenases (COX-1/-2), thrombospondins (TSP-1/-2), urokinase plasminogen activator (uPA) and **matrix** metalloproteases-2 and -9 (MMP-2/-9). As a result of these Ras-regulated changes in gene **expression**, the tumor **cells** cause stimulation of endothelial **cells** in nearby **vascular** beds (directly via VEGF, and indirectly via COX-produced prostaglandins) and promote remodeling of the **extracellular matrix** (by lowering TSP and increasing uPA/MMPs). The latter effect makes growth factors available for endothelial **cell** activation and migration. In addition, tumor **cell**-activated stromal **cells** also contribute to the stimulation of **angiogenesis** by further enhancing the production and secretion of proangiogenic factors into the tumor stroma.

L21 ANSWER 27 OF 36 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2004:221300 BIOSIS
DOCUMENT NUMBER: PREV200400224377
TITLE: Regulation of **angiogenesis** by **extracellular matrix.**
AUTHOR(S): Sottile, Jane [Reprint Author]
CORPORATE SOURCE: Center for Cardiovascular Research, Department of Medicine, University of Rochester Medical Center, 601 Elmwood Avenue, Box 679, Rochester, NY, 14642, USA
jane_sottile@urmc.rochester.edu
SOURCE: Biochimica et Biophysica Acta, (4 March 2004) Vol. 1654, No. 1, pp. 13-22. print.
ISSN: 0006-3002 (ISSN print).
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Apr 2004
Last Updated on STN: 21 Apr 2004

AB During **angiogenesis**, endothelial **cell** growth, migration, and tube formation are regulated by pro- and anti-angiogenic factors, **matrix**-degrading proteases, and **cell-extracellular matrix** interactions. Temporal and spatial regulation of **extracellular matrix** remodeling events allows for local changes in net **matrix** deposition or degradation, which in turn contributes to control of **cell** growth, migration, and **differentiation** during **different** stages of **angiogenesis.** Remodeling of the **extracellular matrix** can have either pro- or anti-angiogenic effects. **Extracellular matrix** remodeling by proteases promotes **cell** migration, a critical event in the formation of new vessels. **Matrix**-bound growth factors released by proteases and/or by angiogenic factors promote **angiogenesis** by enhancing endothelial migration and growth. **Extracellular matrix** molecules, such as thrombospondin-1 and -2, and proteolytic fragments of **matrix** molecules, such as endostatin, can exert anti-angiogenic effects by inhibiting endothelial **cell proliferation**, migration and tube formation. In contrast, other **matrix** molecules promote endothelial **cell** growth and morphogenesis, and/or stabilize nascent **blood vessels.** Hence, **extracellular matrix** molecules and **extracellular matrix** remodelling events play a key role in regulating **angiogenesis.**

L21 ANSWER 28 OF 36 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 2003:515022 BIOSIS
DOCUMENT NUMBER: PREV200300512165
TITLE: **HUMAN** SCLERA GENE **EXPRESSION** PROFILE USING CDNA **MICROARRAY** ANALYSIS.
AUTHOR(S): Young, T. L. [Reprint Author]; Scavello, G. [Reprint Author]; Choi, J.; Rappaport, E.
CORPORATE SOURCE: Divisions of Ophthalmology and Genetics, Children's Hospital Philadelphia, Philadelphia, PA, USA
SOURCE: ARVO Annual Meeting Abstract Search and Program Planner, (2003) Vol. 2003, pp. Abstract No. 411. cd-rom.
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology. Fort Lauderdale, FL, USA. May 04-08, 2003. Association for Research in Vision and Ophthalmology.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)

Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Nov 2003
Last Updated on STN: 5 Nov 2003

AB Purpose: To develop gene **expression** profiles of **human** sclera to allow for the identification of novel, uncharacterized genes, and to identify candidate genes for scleral disorders. Methods: Total RNA was isolated from 6 donor sources of **human** sclerae, and reverse transcribed into cDNA using a T7-(dT)24 primer. Resulting cDNA was in vitro transcribed to produce biotin-labeled cRNA, fragmented, and mixed with hybridization controls before a 16-hour incubation/ hybridization step to oligonucleotide probes on 6 Affymetrix U95A chips. The chips were scanned twice at 570 nM and the data collected using GeneChip software. Array analyses were carried out with **Microarray** Suite, version 5.0 (Affymetrix), using the **expression** analysis algorithm to run an absolute analysis after **cell** intensities were computed. All arrays were normalized to the same target intensity using all probe sets. Reverse- transcription PCR was performed to validate the **microarray** results. Results: Labelled, fragmented scleral cRNA hybridized to more than 58 % of the 12,626 probe sets represented on the **microarray** chip. There were 3769 genes with "present" calls assigned independently to all six **human** scleral samples. These genes could be clustered into 4 major categories: transcription (10%), metabolism (8.8%), **cell** growth and **proliferation** (5.4%), and **extracellular matrix** (2%). Many **extracellular matrix** proteins, such as collagens 6A3 and 10A1, **thrombospondins 2** and 4, versican, and dystroglycan have not previously been shown to be **expressed** in sclera. RT-PCR results confirmed **expression** in 6 of 6 genes examined. Conclusions: This study demonstrates the utility of gene **microarray** technology in identifying global patterns of scleral gene **expression**, and provides the first comprehensive list of genes **expressed** in **human** sclera. Identification of genes **expressed** preferentially or exclusively in sclera contributes to our understanding of scleral biology, and potentially provides positional candidate genes for scleral disorders such as high myopia.

L21 ANSWER 29 OF 36 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
ACCESSION NUMBER: 2002:177888 BIOSIS
DOCUMENT NUMBER: PREV200200177888
TITLE: **Differential** role of alpha4beta1 integrin as a thrombospondin-1 receptor in **human** umbilical vein and **microvascular** endothelial **cells.**
AUTHOR(S): Garcia, Maria J. Calzada [Reprint author]; Sipes, John M.; Krutzsch, Henry C.; Annis, Douglas; Mosher, Deane F.; Roberts, David D.
CORPORATE SOURCE: Laboratory of Pathology, NIH, 10 Center Drive, Bethesda, MD, 20892, USA
SOURCE: Molecular Biology of the Cell, (Nov, 2001) Vol. 12, No. Supplement, pp. 268a. print.
Meeting Info.: 41st Annual Meeting of the American Society for Cell Biology. Washington DC, USA. December 08-12, 2001. American Society for Cell Biology.
CODEN: MBCEEV. ISSN: 1059-1524.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Mar 2002

Last Updated on STN: 6 Mar 2002

L21 ANSWER 30 OF 36 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

ACCESSION NUMBER: 2002:165655 BIOSIS
DOCUMENT NUMBER: PREV200200165655
TITLE: Thrombospondins: Multifunctional regulators of **cell** interactions.
AUTHOR(S): Adams, Josephine C. [Reprint author]
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, MRC Laboratory for Molecular Cell Biology, University College London, Gower Street, London, WC1E 6BT, UK
dmcbjca@ucl.ac.uk
SOURCE: Schekman, Randy [Editor]; Goldstein, Larry [Editor]; McKnight, Steven L. [Editor]; Rossant, Janet [Editor]. Annual Review of Cell and Developmental Biology, (2001) pp. 25-51. Annual Review of Cell and Developmental Biology. print.
Publisher: Annual Reviews, 4139 El Camino Way, Palo Alto, CA, 94303-0139, USA. Series: Annual Review of Cell and Developmental Biology.
ISSN: 1081-0706. ISBN: 0-8243-3117-6 (cloth).
DOCUMENT TYPE: Book
Book; (Book Chapter)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Mar 2002
Last Updated on STN: 5 Mar 2002

L21 ANSWER 31 OF 36 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004382557 EMBASE
TITLE: **Cell-matrix** signaling and thrombospondin: Another link to myocardial **matrix** remodeling.
AUTHOR: Spinale F.G.
CORPORATE SOURCE: F.G. Spinale, Cardiothoracic Surgery, Strom Thurmond Research Bldg., Medical University of South Carolina, 114 Doughty St., Charleston, SC 29425, United States.
wilburnm@musc.edu
SOURCE: Circulation Research, (3 Sep 2004) 95/5 (446-448).
Refs: 30
ISSN: 0009-7330 CODEN: CIRUAL
COUNTRY: United States
DOCUMENT TYPE: Journal; Editorial
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
LANGUAGE: English

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ACCESSION NUMBER: 2003045685 EMBASE
TITLE: Biology of **angiogenesis** in tumors of the gastrointestinal tract.
AUTHOR: Reinmuth N.; Parikh A.A.; Ahmad S.A.; Liu W.; Stoeltzing O.; Fan F.; Takeda A.; Akagi M.; Ellis L.M.
CORPORATE SOURCE: Dr. L.M. Ellis, Department of Surgical Oncology, Univ. TX M.D. Anderson Cancer Ctr., 1515 Holcombe Blvd.-444, Houston, TX 77030-4009, United States.
lellis@mdanderson.org
SOURCE: Microscopy Research and Technique, (1 Feb 2003) 60/2

(199-207).
Refs: 102
ISSN: 1059-910X CODEN: MRTEEO
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The realization that the growth and spread of tumors are dependent on **angiogenesis** has created new avenues of research designed to help us to better understand cancer biology and to facilitate the development of new therapeutic strategies. However, the process of **angiogenesis** consists of multiple, sequential, and interdependent steps with a myriad of positive and negative regulators of **angiogenesis** being involved. The survival of tumors and thus their metastases are dependent upon the balance of endogenous angiogenic and anti-angiogenic factors such that the outcome favors increased **angiogenesis.** Several growth factors have been identified that regulate **angiogenesis** in cancers of the gastrointestinal tract. These include pro-angiogenic factors like **vascular** endothelial growth factor (VEGF) and anti-angiogenic factors, i.e., thrombospondin. The following review provides a brief overview about the most important factors that are involved in the angiogenic process in tumors derived from colon, stomach, and pancreas. A thorough understanding of the role these factors play in the angiogenic process may lead to the development of novel therapeutic antineoplastic strategies. .COPYRGT. 2003 Wiley-Liss, Inc.

L21 ANSWER 33 OF 36 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002390135 EMBASE
TITLE: **Matricellular** proteins: **Extracellular** modulators of **cell** function.
AUTHOR: Bornstein P.; Sage E.H.
CORPORATE SOURCE: P. Bornstein, Department of Biochemistry, Box 357350, University of Washington, Seattle, WA 98195, United States. bornsten@u.washington.edu
SOURCE: Current Opinion in Cell Biology, (1 Oct 2002) 14/5 (608-616).
Refs: 70
ISSN: 0955-0674 CODEN: COCBE3
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The term '**matricellular**' has been applied to a group of **extracellular** proteins that do not contribute directly to the formation of structural elements in vertebrates but serve to modulate **cell-matrix** interactions and **cell** function. Our understanding of the mode of action of **matricellular** proteins has been advanced considerably by the recent elucidation of the phenotypes of mice that are deficient in these proteins. In many cases, aspects of these phenotypes have illuminated previously unsuspected consequences of the lack of appropriate interactions of **cells** with their environment.

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ACCESSION NUMBER: 2002171307 EMBASE
TITLE: **Matrix** metalloproteinases and **angiogenesis.**
AUTHOR: Jackson C.
CORPORATE SOURCE: Dr. C. Jackson, Sutton Arthritis Research Laboratory, Royal North Shore Hospital, St. Leonards, NSW 2065, Australia. cjackson@med.usyd.edu.au
SOURCE: Current Opinion in Nephrology and Hypertension, (2002) 11/3 (295-299).
Refs: 48
ISSN: 1062-4821 CODEN: CNHYEM
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
028 Urology and Nephrology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **Angiogenesis** is a prominent feature of numerous diseases, including cancer and arthritis, and appears to play an important role in kidney disease and hypertension. The **matrix** metalloproteinases, especially **matrix** metalloproteinase-2, play a vital role during **angiogenesis** by degrading the surrounding **extracellular matrix** and allowing endothelial **cell** invasion. Membrane type 1 **matrix** metalloproteinase directly degrades **matrix** components as well as activating **matrix** metalloproteinase-2 on the **cell** surface. The integrin receptors, particularly α(v)β(3), can recruit and possibly activate **matrix** metalloproteinases to localized **microdomains** on the **cell** membrane. This restricts **matrix** metalloproteinase activity to the **pericellular** region, preventing excessive **matrix** degradation which would otherwise impede endothelial invasion. Inhibitors of **matrix** metalloproteinase activity may actually promote **cell** invasion by preventing uncontrolled **matrix** degradation. In addition to degrading the **matrix**, **matrix** metalloproteinases produce protein fragments that impede their angiogenic action. These multiple regulatory pathways permit fine control over **cell** invasion during **angiogenesis** and provide new, precise strategies for targeting abnormal **angiogenesis**, through control of **matrix** metalloproteinase activity. .COPYRGT. 2002 Lippincott Williams & Wilkins.

L21 ANSWER 35 OF 36 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001422512 EMBASE
TITLE: Single nucleotide polymorphisms in multiple novel thrombospondin genes may be associated with familial premature myocardial infarction.
AUTHOR: Topol E.J.; McCarthy J.; Gabriel S.; Moliterno D.J.; Rogers W.J.; Newby L.K.; Freedman M.; Metivier J.; Cannata R.; O'Donnell C.J.; Kottke-Marchant K.; Murugesan G.; Plow E.F.; Stenina O.; Daley G.Q.
CORPORATE SOURCE: Dr. E.J. Topol, Dept. of Cardiovascular Medicine, Desk F25, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, United States. topole@ccf.org
SOURCE: Circulation, (27 Nov 2001) 104/22 (2641-2644).

Refs: 24
ISSN: 0009-7322 CODEN: CIRCAZ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Background - Recent advances in high-throughput genomics technology have expanded our ability to catalogue allelic variants in large sets of candidate genes related to premature coronary artery disease. Methods and Results - A total of 398 families were identified in 15 participating medical centers; they fulfilled the criteria of myocardial infarction, **revascularization**, or a significant coronary artery lesion diagnosed before 45 years in men or 50 years in women. A total of 62 **vascular** biology genes and 72 single-nucleotide polymorphisms were assessed. Previously undescribed variants in 3 related members of the thrombospondin protein family were prominent among a small set of single-nucleotide polymorphisms that showed a statistical association with premature coronary artery disease. A missense variant of thrombospondin 4 (A387P) showed the strongest association, with an adjusted odds ratio for myocardial infarction of 1.89 (P=0.002 adjusted for covariates) for individuals carrying the P allele. A variant in the 3' untranslated region of **thrombospondin**-2 (change of thymidine to guanine) seemed to have a protective effect against myocardial in individuals homozygous for the variant (adjusted odds ratio of 0.31; P=0.0018). A missense variant in thrombospondin-1 (N700S) was associated with an adjusted odds ratio for coronary artery disease of 11.90 (P=0.041) in homozygous individuals, who also had the lowest level of thrombospondin-1 by plasma assay (P=0.0019). Conclusions - This large-scale genetic study has identified the potential of multiple novel variants in the thrombospondin gene family to be associated with familial premature myocardial infarction. Notwithstanding multiple caveats, thrombospondins specifically and high-throughput genomic technology in general deserve further study in familial ischemic heart disease.

L21 ANSWER 36 OF 36 EMBASE
on STN

ACCESSION NUMBER: 95085244 EMBASE
DOCUMENT NUMBER: 1995085244
TITLE: Thrombospondins.
AUTHOR: Bornstein P.; Sage E.H.
CORPORATE SOURCE: Department of Biochemistry, University of Washington,Seattle, WA 98195, United States
SOURCE: Methods in Enzymology, (1995) 245/- (62-85).
ISSN: 0076-6879 CODEN: MENZAU
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
018 Cardiovascular Diseases and Cardiovascular Surgery
021 Developmental Biology and Teratology
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English

=> d ibib abs ind l5 1-2

L5 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:288678 HCAPLUS
DOCUMENT NUMBER: 137:149896
TITLE: Systemic inhibition of tumor growth and angiogenesis by thrombospondin-2 using cell-based antiangiogenic gene therapy
AUTHOR(S): **Streit, Michael; Stephen, Antonia E.** ; Hawighorst, Thomas; Matsuda, Kant; Lange-Asschenfeldt, Bernhard; Brown, Lawrence F.; **Vacanti, Joseph P.; Detmar, Michael**
CORPORATE SOURCE: Cutaneous Biology Research Center and Department of Dermatology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, 02129, USA
SOURCE: Cancer Research (2002), 62(7), 2004-2012
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent studies indicate that continuous administration improves the antitumoral efficacy of angiogenesis inhibitors, as compared with intermittent dosing, suggesting a potential role of gene therapy in antiangiogenic tumor therapy. We established a tissue-engineered implant system for the continuous in vivo production of thrombospondin-2 (TSP-2), a potent endogenous inhibitor of tumor growth and angiogenesis. Fibroblasts were retrovirally transduced to overexpress TSP-2 and were seeded onto biodegradable polymer scaffolds. After transplantation into the peritoneal cavity of nude mice, bioimplants maintained high levels of TSP-2 secretion over extended time periods, resulting in increased levels of circulating TSP-2. Bioimplant-generated TSP-2 potently inhibited tumor growth and angiogenesis of human squamous cell carcinomas, malignant melanomas, and Lewis lung carcinomas that were implanted at a distant site. These results provide the first proof-of-principle for the feasibility and therapeutic efficiency of systemic, cell-based antiangiogenic gene therapy using biodegradable polymer grafts for the treatment of cancer.

CC 1-6 (Pharmacology)
Section cross-reference(s): 3

ST antiangiogenic thrombospondin gene therapy human melanoma lung cancer inhibitor

IT Lung, neoplasm
(carcinoma, Lewis, inhibitor of; systemic inhibition of tumor growth and angiogenesis by thrombospondin-2 using cell-based antiangiogenic gene therapy)

IT Intestine
(colon; systemic inhibition of tumor growth and angiogenesis by thrombospondin-2 using cell-based antiangiogenic gene therapy)

IT Melanoma
(inhibitor; systemic inhibition of tumor growth and angiogenesis by thrombospondin-2 using cell-based antiangiogenic gene therapy)

IT Lung, neoplasm
(squamous cell carcinoma, inhibitor; systemic inhibition of tumor growth and angiogenesis by thrombospondin-2 using cell-based antiangiogenic gene therapy)

IT Angiogenesis inhibitors
Antitumor agents
Apoptosis
Blood vessel
Gene therapy

Human
Liver
Ovary
Peritoneum
Spleen
Uterus
(systemic inhibition of tumor growth and angiogenesis by thrombospondin-2 using cell-based antiangiogenic gene therapy)

IT Thrombospondins
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(systemic inhibition of tumor growth and angiogenesis by thrombospondin-2 using cell-based antiangiogenic gene therapy)

IT Liver
(toxicity; systemic inhibition of tumor growth and angiogenesis by thrombospondin-2 using cell-based antiangiogenic gene therapy)

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:143280 HCAPLUS
DOCUMENT NUMBER: 136:189386
TITLE: Delivery of thrombospondin from implantable tissue matrices
INVENTOR(S): **Detmar, Michael; Vacanti, Joseph P. ; Streit, Michael; Stephen, Antonia E.**
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 16 pp., Cont.-in-part of U.S. Ser. No. 536,087.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2002022592	A1	20020221	US 2001-822161		20010330
US 2002031500	A1	20020314	US 2001-770339		20010126
US 6692738	B2	20040217			
US 2004086497	A1	20040506	US 2003-690077		20031021
PRIORITY APPLN. INFO.:			US 1999-127221P	P	19990331
			US 2000-178842P	P	20000127
			US 2000-536087	A2	20000324
			US 2001-770339	A2	20010126

AB Normal cells, such as fibroblasts or other tissue or organ cell types, are genetically engineered to express biol. active, anti-angiogenic compds., in particular, thrombospondin-2. These cells are seeded into a matrix for implantation into the patient to be treated. Cells may also be engineered to include a lethal gene, so that implanted cells can be destroyed once treatment is completed. Cells can be implanted in a variety of different polymer matrixes. In a preferred embodiment, these matrixes are implantable and biodegradable over a period of time equal to or less than the expected period of treatment, during which the engrafted cells form a functional tissue producing the desired biol. active agent for longer periods of time. These devices and strategies are used as delivery systems, which may be implanted by standard or minimally invasive implantation techniques, for delivery of anti-angiogenic mols., especially thrombospondin-2, for the treatment of a variety of conditions that produce abnormal growth,

including treatment of malignant and benign neoplasias, vascular malformations (hemangiomas), inflammatory conditions, keloid formation and adhesion, endometriosis, congenital or endocrine abnormalities, and other conditions that can produce abnormal growth such as infection. Bioimplants maintained TSP-2 secretion over prolonged time periods, resulting in a potent inhibition of tumor growth and angiogenesis of three different, highly aggressive malignant tumors implanted at a distant site.

IC ICM A61K045-00
ICS A61K038-48
NCL 514012000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
ST thrombomodulin delivery implantable tissue matrix
IT Thrombomodulin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(2; delivery of thrombospondin from implantable tissue matrixes)
IT Eye
(angiogenesis; delivery of thrombospondin from implantable tissue matrixes)
IT Polymers, biological studies
RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biodegradable; delivery of thrombospondin from implantable tissue matrixes)
IT Artery, disease
(coronary, restenosis; delivery of thrombospondin from implantable tissue matrixes)
IT Adhesion, biological
Angiogenesis inhibitors
Antirheumatic agents
Antitumor agents
Cell proliferation
Fibroblast
Keloid
Multiple sclerosis
Psoriasis
Stem cell
Transformation, genetic
(delivery of thrombospondin from implantable tissue matrixes)
IT Polymers, biological studies
Thrombomodulin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(delivery of thrombospondin from implantable tissue matrixes)
IT Gland
(endocrine; delivery of thrombospondin from implantable tissue matrixes)
IT Uterus, disease
(endometriosis; delivery of thrombospondin from implantable tissue matrixes)
IT Polyester fibers, biological studies
RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glycolic acid; delivery of thrombospondin from implantable tissue matrixes)
IT Drug delivery systems
(implants; delivery of thrombospondin from implantable tissue matrixes)
IT Skin, disease
(proliferative; delivery of thrombospondin from implantable tissue matrixes)
IT Collagens, biological studies

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(type I; delivery of thrombospondin from implantable tissue matrixes)

IT 26009-03-0, Polyglycolic acid 26124-68-5, Polyglycolic acid
RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fiber; delivery of thrombospondin from implantable tissue matrixes)